TISANI VERLAG

WEST-SYNDROME - A CASE OF SEVERE VACCINATION DAMAGE AND ITS HOMEOPATHIC CURE

Dr.-Ing. Joachim-F. Grätz, Oberhausen i. Obb., Germany

Translated by Katja Schütt (Germany) and Dr. Firuzi Mehta (India)

This case of severe vaccination damage is representative for many other injuries from immunization, which often lead to life-long disability.
It is meant to encourage affected parents and to demonstrate, that even severe vaccination damages can be alleviated or cured.
However, it should be remembered that *homeopathy treats each patient individually,* and that no sure prognosis about a complete cure (restitutio ad integrum) can be given in advance.

West-Syndrome

The *West-Syndrome* is an infantile epileptic *encephalopathy*, which was first described by the English physician William James West. It is composed of the following triad:

1. Infantile spasms.
2. An interictal EEG pattern termed hypsarrhythmia.
3. Mental retardation, although the diagnosis can be made even if one of the 3 elements is missing (according to the international classification).

The prognosis is mainly determined by the type of encephalopathy underlying the condition, but usually unfavorable.

Nick, 9 months old

Nick is suffering from epileptic seizures for about five months, which are hardly influenced by strong anti-epileptic drugs. He was in a very bad condition when introduced during the first consultation.

Until his fourth month of age Nick had been “a little sunshine”, cheerful and happy. He started speaking quite early, and could also control his head very early – the first important step for postural maturity (development of body erection). Nick even grew 10 cm (4 inches) during the first four weeks.

During one of the check-ups he got the almost mandatory vaccinations against diphtheria, tetanus and polio, which he seemed to tolerate quite well in the beginning. But a few days after the vaccination he got increasingly restless and slept less. The convulsions started on the 15th day after the vaccinations. The first fit started with a nightly piercing cry, that is an evident sign for an encephalopathy. Since then the convulsions appeared very frequently, regularly at

the beginning, and at certain times, mainly after waking. His head control vanished completely after being vaccinated.

The convulsions showed varying symptom patterns. Once there was a slight twitching of the shoulders (one-sided or on both sides at times), sometimes accompanied by rolling of the eyes, trembling of eyes, lost head control or raising the left or right arm. Often, the head fell forward (head nodding fits), the arms twitched or got stiff. Sometimes there were only reactions of the pupils or a fixed gaze. The fits appeared at short intervals. At times, Nick was laughing or moaning at the end or after the fits.

The physicians of a famous children's hospital diagnosed West-Syndrome. That means: BNS convulsions, psychomotor development disturbances and hypsarrhythmia. The EEG was abnormal and severely pathological, "like in severely disabled children". The neurological examination revealed developmental retardation. Anti-epileptic drugs and barbiturates were prescribed, and nothing further could be done for him.

The homeopathic case anamnesis revealed further symptoms, proving the logic of the case. As Dr. Eichelberger, a well known German homeopathic doctor, said, "A healthy person does not become ill". The deeper meaning of this sentence is, that a strong miasmatic load of the child, inherited from parents or other relatives, is underlying each disease, and especially severe pathologies. That is to say, they are due to the underlying chronic disease, i.e. miasms, on whose terrain all diseases grow, and which are to be eliminated. [For more details see *"Sanfte Medizin – Die Heilkunst des Wassermannzeitalters"*, Grätz, J.-F., Tisani Verlag, Oberhausen i. Obb., Germany]

Sycosis, one of the four principal miasms, was already active since the first days of life. For months Nick suffered from severe colics and sleeping disorders, "it was always difficult to get him to bed", "since the age of two he slept much worse", his eyes were glued, "Nick was born with glued eyes", and infantile coryza.

Nick always startled easily, from noises behind him, but even from hearing the water running. He also startled often during sleep. Nick is very sensitive, and as his mother said "our mood barometer". He was crying when his therapy was discussed in the hospital. This convinced his mother that he should not take ACTH, a hormone of the pituitary gland. She had often observed such "presentiments".

Another striking feature was also the constant restlessness of his arms and legs, what was "different than normal kicking his feet und waving his arms about". Usually, he had clammy and smelly feet. The toenails were slightly bending upwards, the hands often "clenched", and the thumbs clenched inward.

At full moon Nick was extremely restless, especially in the evening and at night. Moreover, he feared the dark, like his mother. When waking up at night he could only fall asleep again when the light was on. His preferred sleeping position was on the abdomen.

Only once there was a severe cold, but without much fever (max. 37,5° C). Twice the boy had a coryza, once he ameliorated quite soon when being on the seashore (North Sea). His face was pale and whitish, "deathly pale" at times, and there was a "stork bite" (Unna's nevus) above the root of the nose.

Pregnancy:
Nick's mother suffered from extreme nausea for four months. There was spotting during the third month of pregnancy, which was treated with bed rest and magnesium supplements. She feared losing her child, and her fear of darkness, from which she suffered since childhood, increased tremendously. Her physician diagnosed "bad hormone levels" and prescribed progesterone-substitutes. Her legs were swollen during the last four weeks, especially the lower legs and ankles ("as usual during menses"). She had an abortion before being pregnant with Nick.

Family:
Mother: Infantile rheumatism, penicillin allergy, menstrual disturbances, depression, abortio, cystitis, pyelitis, frequent vaginitis, mastitis twice during lactation. All of these are clear signs of the sycotic miasm.
Father: Premature birth (at 7 months), he never crawled according to his mother. Retarded motor development. Frequent gastro-intestinal infections with nausea, vomiting, flatulence and diarrhea. Paresthesia in forearms and hands in the morning. Frequent severe influenzal infections, mostly without fever. Moreover, the family history revealed tuberculosis, pneumonia, depression, migraine, kidney stones, alcoholism, ovarian cysts, diabetes, breast cancer, rheumatism and hip surgery.

Remedy choice (see repertorization): Medorrhinum LM18, 1 drop in a spoonful of water, every third day in the morning.

Results: Seven days after Nick started taking Medorrhinum I got the following report: Red spots between the eyebrows appeared already after the first dose, "the same as his grandma had". His convulsions aggravated in the afternoon, and in the evening pimples appeared on the left cheek. Days later he became increasingly hypotonic. Moreover, there appeared a stubborn, thick milk crust on the head.

The second dose caused increased restlessness. Nick became more fidgety. A skin rash appeared on the whole face, like neurodermatitis on the cheeks and around the eyes, and like psoriasis on the chin. Both remained for four weeks! Moreover, dentition started now. The duration of the fits got longer, the boy got very tired, but more awake and fidgety in the evening. Coryza appeared with a copiously flowing discharge for the first time! Later, the convulsive disposition decreased and Nick got a real fever (38,5° C) for the first time in his life, a further positive sign of his development.

Nick's motor function ameliorated already after the third dose of Medorrhinum. He could hold up better, and also his head control improved considerably. But the psoriasis as well as neurodermatitis got worse. Also a diaper rash appeared. But Nick laughed much more and was cheerful!

These were slight signs of a cure! According to Hering's law of cure from within out (skin eruptions, however central amelioration). Hering's law of cure states, that cure always proceeds from within out, from the head down and in the reverse order as the symptoms have appeared in the body. Cure also proceeded according to the law of biphasic diseases, the condition in the vagotone healing phase (increased convulsions, skin eruptions, increased tiredness, fever). [For more details see *"Sind Impfungen sinnvoll? – Ein Ratgeber aus der homöo-*

pathischen Praxis",Grätz, J.-F., 8th edition 2005, Tisani Verlag, Oberhausen i. Obb., Germany]

ComRep V8.5

No.	Symptoms
1	Mind - fear, dark
2	Mind - restlessness, nervousness
3	Mind - starting,startled - fright / noise, from
4	Mind - starting, startled - sleep - during
5	Mind - clairvoyance
6	Mind - laughing - convulsions, before, during or after
7	Head - falling of head forward /heaviness
8	Sleep - sleeplessness - sleepiness, with
9	Sleep - position - abdomen
10	Generalities - sycotic constitution
11	Generalities - reaction, lack of
12	Generalities - convulsions - epileptic
13	Modalities - vaccination, after
14	Modalities - moon - full
15	Modalities - air - seashore - amel.
16	Face - discoloration - pale / sickly
17	Chest - lungs - tuberculosis
18	Extremities - coldness - foot
19	Extremities - perspiration -foot
20	Extremities - restlessness - arms
21	Extremities - restlessness - legs
22	Extremities - position - fist - spasmodic bending of fingers into a fist
23	Extremities - position - clenching thumbs
24	Extremities - nails - spoon nails
25	Eyes - lids - glued - morning
26	Stomach ache - diarrhea - during (colic)

Method: matches

No.	Remedies	Neg	Total	Symptoms: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
1	sulf	8	46	.	3	2	2	.	.	3	2	.	2	3	3	3	3	.	3	3	3	3	.	2	.	1	.	3	2
2	calc	9	39	2	3	2	.	1	.	2	2	1	2	3	3	.	2	.	3	3	3	3	.	.	.	.	.	3	1
3	sep	9	38	.	3	2	2	.	.	2	3	.	3	2	2	.	2	.	3	2	3	3	1	2	.	.	.	2	1
4	**med**	4	38	2	2	2	2	1	.	1	1	1	3	3	2	1	.	1	3	2	2	1	.	1	2	.	1	3	1
5	lyc	7	38	2	3	2	1	.	.	2	1	.	2	2	2	.	2	.	3	3	3	3	1	2	1	.	.	1	2
6	bell	10	38	.	3	3	3	.	.	2	3	2	.	.	3	.	2	.	2	.	3	2	.	2	2	2	.	2	2
7	ars	6	38	.	3	1	2	.	.	2	1	1	.	2	2	2	1	.	3	2	3	2	1	3	2	1	.	2	2
8	sil	10	37	.	3	3	2	1	.	2	2	.	2	.	3	3	3	.	2	3	3	3	1	.	.	.	.	1	.
9	caust	8	37	2	2	2	3	.	2	1	2	.	2	1	3	.	1	.	2	.	3	2	3	2	.	2	.	2	.
10	phos	8	34	2	1	2	2	2	.	2	3	.	.	2	2	.	.	.	2	3	3	2	1	2	1	.	.	1	1
11	merc	9	32	.	3	2	2	.	.	2	2	.	1	2	1	.	.	.	2	2	3	3	1	.	2	1	.	2	1
12	stram	10	31	3	3	3	2	1	1	1	2	2	.	2	3	.	.	.	2	.	3	.	1	.	.	1	.	.	1
13	puls	12	30	2	3	.	2	.	.	2	3	1	1	.	2	.	.	.	2	3	3	3	.	.	.	.	.	2	1
14	nit-ac	11	30	.	2	3	2	.	.	3	1	.	3	.	2	.	.	.	2	2	3	2	.	1	.	.	2	1	1
15	kali-c	12	30	.	2	3	.	.	.	1	2	.	1	2	2	.	.	.	2	3	3	2	.	3	.	.	.	2	2
16	cupr	14	30	2	3	.	.	.	.	2	2	.	.	2	3	.	.	.	3	.	3	2	.	.	3	3	.	.	2
17	carb-v	10	30	2	2	2	1	.	.	3	1	.	1	3	1	.	.	.	3	2	2	3	.	1	.	.	.	2	1
18	nat-m	13	28	.	2	3	.	.	.	3	2	.	.	1	2	.	.	1	3	2	3	2	.	2	.	.	.	2	.
19	lach	12	27	.	2	2	.	1	.	3	2	.	2	2	2	.	.	.	2	2	3	1	.	.	1	2	.	.	.
20	graph	12	27	.	2	.	1	.	.	1	1	.	2	2	.	.	2	.	3	2	3	3	.	1	.	.	.	3	1

Repertorization

After some more doses of the "magic drops", as Nick's mother called them, constipation appeared temporarily, later on fever again, this time even one degree higher – a very good development, as the boy appeared to come out of his condition of lack of reaction. The eyes were glued twice a week, once so severe, that Nick could not open his eyes for three days. Also, his

navel started to suppurate again, "like at that time when he was a baby", but only for a few days. All in all, positive signs of cure, and of a "rewinding process", as homeopaths observe again and again.

But now, the mother reported, everything was over. The skin was clear again, eyes negative, and – lo and behold – with the cure of the stubborn skin rash no further convulsions appeared! Nick is again a normal child and develops well. As if something abnormal had never happened. His mother was overwhelmed with joy.

Of course, his chronic treatment in the sense of a basic homeopathic treatment was not finished yet, as the primary aim is and must be the cure of all miasms. Regarding the observations on the effects of the vaccination, our duty is carried out completely, as the vaccinosis, i. e. the disease which is due to the vaccine, was treated successfully. The convulsions did not reappear after reducing and stopping the antiepileptic drugs. But there is still something to do. Only his symptom picture will tell us when his anti-miasmatic treatment will be finished. Only then, after about two to three years, will he be discharged from the homeopathic practice. But it is sure: Nick will never be vaccinated again!

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(A shortened version was published in Dr. Chris Gaublomme's *International Vaccination Newsletter*, 1995, Belgium.)

See also the essay/article "Vaccinations – A Danger to Health?":
www.tisani-verlag.de/Vaccinations-DangerToHealth_e.pdf

Dr. Joachim-F. Grätz is an internationally recognized homeopath, very well known in German-speaking areas. He has written several books about Classical Homeopathy including the chronic miasms, vaccination damages und their homeopathic cure as well as about 100 essays/articles in magazines and homeopathic journals.

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VACCINATIONS

A DANGER TO HEALTH?

Dr. Joachim-F. Grätz, Oberhausen i. Obb., Germany

The theme of vaccination is currently more relevant than ever before in history. Large-scale and often aggressive propaganda campaigns in the media, even in special kindergarten magazines, try to play down its danger by reducing it to a "harmless prick". Only a few people know that this is not the case and that greater dangers lie in vaccinations than have been realized so far – not only for the individual but also for mankind.

From observations and experience over a long period of years we can see that people are becoming increasingly ill from generation to generation. Just think of the many children suffering from neurodermatitis, spastic bronchitis, asthma, hay fever, dyslexia, hyperactivity and physical and/or mental disabilities. Later – in puberty – there are the additional, ever increasing problems concerning reproduction (menstruation complaints, genital mycosis, tubal pregnancy, miscarriages, and premature births, reduced sperm motility to mention but a few) culminating in absolute sterility. All this was not existent to this degree in the last generation, let alone the one before. If they continue in the same way humanity is steering headlong towards the greatest biological catastrophe, the danger of robbing itself of the capability to reproduce!

A great percentage of the damages mentioned above must be blamed on the highly praised vaccinations, as can be proved again and again on the basis of many casuistics in homeopathy. We are all steering towards a global catastrophe, if we do not learn to take on an individual responsibility for our health, our most precious asset. It is in fact a process which is gradually making slow progress, yet drops of water can erode rock formations. Each successive generation will be more affected than the previous one.

REACTIONS TO VACCINATION AND RESULTING DAMAGE

It does not take an opponent of vaccination to notice, time and time again, that children are disturbed in their general constitution after any kind of vaccination – any honest and down to earth observer with normal common sense can see it for hirnself. Vaccinated children are generally more likely to catch infectious diseases than those who have not been vaccinated, the reactions to vaccinations can be varied; the scale ranges from "none" to the gravest forms of encephalitis (inflammation of the brain) or meningitis (inflammation of the meninge) with resulting dementia.
Comparatively harmless reactions are a high temperature, sensitivity and inflammation where the injection was given, but there are more and more incidents of complications which can

last a short time or (as is mostly the case), can be permanent. A frequent cause of maladjusted behavior, such as hyperactivity, aggressivity or other general "retarded developments" – children learn to speak later and often insufficiently, they are sometimes hardly able to read or write (dyslexia) – can be traced back to previous vaccinations. Also neurodermatitis or hay fever and infant's asthma can often be linked to a vaccination. Children who were initially completely satisfied and "easy to care for" change – often the change can never be reversed. This all begins at a time when the vaccination program begins.

Generally we do not speak of *vaccination damage* (the authorities that is) until dramatic harm is visible, which is obvious to anyone and where the connection to vaccination can no longer be denied. Only these cases are officially recognized. But this is only the tip of the iceberg according to many critics. Vaccination damage can follow immediately after the vaccination, it can occur a few days or weeks later, often even months or years later. Unfortunately there are deaths too. The sudden infant death syndrome (SIDS) which seems to have no explanation for orthodox medicine is thought by many researchers to have an obvious connection to vaccinations – especially *whooping cough*.

REACTIONS TO VACCINATION IN YOUNG BABIES

With young babies and infants vaccination damage which leads to impairments of the brain and thereby causing motoric and/or mental disability, is usually difficult to discern, because symptoms of illness cannot be expressed at this age, and certain specific signs of illness are still not manifested. The brain, because of its lack of maturity, is not able – up to about the end of the third year – to react to the damage caused by the vaccination in any special way (inflammation). The reason for this is that the myelinization process has not reached its final point i.e. the separate nerve fibers in the central nervous system have not been fully surrounded with myelin, in other words insulated against "shortcircuit". It is only after this point that all symptoms belonging to a postvaccinal encephalitis (inflammation of the brain) can definitely be proved.

In Germany the children are vaccinated at a very early age – before the "encephalitis phase" is reached. The possible form of reaction can therefore express itself "only" as *postvaccinal encephalitis* which shows little or no symptoms in the acute phase and is thus very difficult to recognize. It can also result in later forms of damage to a much greater degree (e. g. hyperactivity, autism, learning difficulties, retarded development) which *Coulter* clearly proves in his book *"Vaccination, Social Violence, and Criminaliaty: The Medical Assault on the American Brain"* and describes as forms of the *postencephalitic syndrome*, a collective term for the damage which occurs in a slight or a more serious illness of the brain accompanied by physical, psychological and mental deficiencies. Cases like these used to occur very rarely; a cluster of illnessses occurred only as a result of epidemic encephalitis (as e. g. between 1919 and 1928) where permanent damage like this was caused. What gives rise to fear is that serious long-term neurological consequences need not necessarily be accompanied by strong reactions to previous vaccinations. This means for the homeopathic anamnesis in chronic cases that when parents often say "All vaccinations were well tolerated", it is in principle worth nothing as an indicator. The miasmatic stigma can have taken place long since completely un-

noticed, and it is not until much later, sometimes after years or even decades, that they become evident to the full extent.

Vaccinations thus always affect the brain whether we are aware of it or not. They interrupt the process of myelinization or can even reverse this process. That means, that vaccine reactions, including serious vaccination damage, are primarily of a neurological nature (demyelinating encephalitis) and can hardly be influenced by psychotherapy or similar treatment, and healing is therefore a forlorn hope.

Seen in this way hyperactivity, dyslexia, aggressivity, elective mutism, autism to name but a few, must be regarded in a completely different light. According to the author these are all neurological disturbances of the brain in differing degrees of manifestation. There are no clear cut borders between hyperactivity, behavioral and/or perceptive disturbances or autism. There are only precise academic differences since each individual symptom is put into a different illness category without bothering about the cause. Looking at it from the standpoint of the brain as an organ it is one and the same phenomenon; neurological "short-circuits" in the brain due to insufficient myelinization but manifested in different regions and in different degrees of severity.

How can such severe reactions and irreparable damage result where the public is normally granted no insight into the matter? Is there a kind of logic behind it, a system, or are these just isolated accidents and coincidences? The question sounds almost heretical: Is it not a false sense of security produced by vaccination? Can vaccination help at all, or does it – on the contrary – bring great danger for the whole of mankind? The concept of vaccinating is based on a completely mistaken idea of how our immune system works. In fact there is no such training of the immune system in the way this has been imagined so far. Introducing inactivated or weakened pathogens or toxins (such as metabolites from pathogens) does not enable the organism to actively come to terms with a slighter form of the illness in order to teach the cells how to build up a specific immunity against the illness.

QUESTIONABLE PROTECTION BY VACCINATION

Many independent researchers of vaccination concur that inoculation does not protect from the illness against which it is applied. If an infection occurs despite an inoculation it is often much more severe and the danger of brain or organ damage much higher. Pediatricians who decided to stop inoculating confirm this. One often hears from them that the children are generally more healthy since vaccinations were stopped. Surely this is not propaganda, since one does not earn more by not inoculating.

In the U.S.A., mass outbreaks of measles occur in schools where 99 % of the pupils are inoculated. This has been confirmed by the *U. S. Centers of Disease Control*. Such phenomena are not new, however. and have been known since the start of mass vaccinations against smallpox (i. e. from the very beginning). From Saxony it is reported that in the early nineteenth century there were repeatedly cases where vaccinated persons fell ill with smallpox after all, that there were epidemics among populations of which almost nine tenths had been inoculated!

Further it can be observed that an inoculation increasingly hinders normal infections and natural immunization in childhood causing the disease to break out later in puberty or even adulthood. Past childhood, however, all childhood diseases are considerably more dangerous and often develop complications, which we homeopaths are very often faced with. Such a shifting was documented for smallpox as far back as 120 years ago. Advocates of vaccinations had to admit that smallpox, "hitherto exclusively a children's disease, now predominantly (80-90 % of all illnesses) attacks adults".

I think we slowly are beginning to realize that the effect of vaccinations does not live up to our previous conceptions, and that by uncritically adopting hypotheses we fell victim to systematic conditioning which has been perpetrated for decades. Our education has made us blind towards any analysis of such correlations, although this is one of the keys to many problems of our time.

VACCINATION FROM FHE POINT OF VIEW OF CLASSICAL HOMEOPATHY

Famous students of Hahnemann already pointed out the "dangers of the smallpox vaccine" when the latter was still alive (1831). Today homeopathy can rely on almost 200 years of experience in treating vaccination side-effects and complications. Homeopathy is an experiential therapy and is based upon natural laws which Hahnemann had verified and described to perfection.

Let us recall the basic pillars:

- the spiritual life force that in the case of illness got out of balance;
- the simile-principle;
- the dematerialized remedies which are administered according to the simile-principle and cause the life force again to resonate in harmony.

In chronic diseases it gets a bit more complicated, because hereditary and acquired miasms playa central role. All chronnic states stem from four basic illnesses, the *miasms* (see insert). By eliminating these miasms step by step with the aid of classical homeopathy the organism regains health – and enduring, (almost) absolute health at that.

Each of these miasms has its typical phenotype which a trained homeopath can recognize with the following criteria: present symptoms, previous illnesses, taking into consideration influences from all blood relations. Often several miasms are present in the organism of a person, so the chronic therapy has to be done with a series of remedies. Today, the majority of people are multimiasmic, whereby some miasms might be latent to differing degrees. This is becoming increasingly worse from generation to generation through heredity factors.

Now an inoculation can activate the miasmic predisposition – often sycotic or tuberculous – which the child inherited from its parents. The latent sycotic or tuberculous miasm – at first hardly noticeable – breaks out and takes on many forms. Often it links up to another active miasm, which already puts a strain on the infant, and thus causes tremendous damage. Reactions to vaccinations therefore belong to a specific type of chronic basic disease.

Since the domain of homeopathy is the healing of chronic diseases of any kind, it is able – now talking of vaccination – to turn the activating process described above back. Mostly, the

miasmic predisposition can be completely eliminated, so that the prognosis is quite positive and often the children show no abnormalities. Insurmountable difficulties usually appear only when for years orthodox therapy with heavy medication had been tried or severe operations had been deemed necessary. But even then relatively good results can be achieved with homeopathy!

THE MIASM

*The **disease behind the disease**. A fixed term in homeopathy describing the character of a chronic basic disease. Four miasms are recognized which are either inherited or acquired during one's life: the psora, the sycotic, the syphilitic and the tuberculous constitution. All chronic states are based upon those four miasms. Now there is a fifth miasm that is purely artificial: the drug miasm (due to the administration of strong drugs for years). A successful homeopathic therapy of chronic diseases can only be attained by checking these miasms first, for they never have the tendency to heal by themselves. They are always present and progress continuously, often insidiously and with many latent phases.*

The chronic first anamnesis of an adult needs a lot of time and sometimes lasts anything up to 2 to 2.5 hours, for babies and children 1 to 1.5 hours. This includes a detailed description of the present ailments as well as the development of the patient from early childhood onwards until today – not just where illnesses are concerned, but also in a global context that has shaped and influenced the individual character spiritually and mentally. Further the family's influence upon the patient, the so-called miasmic predisposition going back to grandfather and great-grandfather, has to be checked before a wellfounded homeopathic treatment can be begun – something unique among all the world's therapy forms. An extensive family anamnesis is performed in order to recognize the inner logic of the illnesses and ailments.

HOMEOPATH'S CASE REPORT

Little Nick is a very convincing example. About two weeks after having been given the *triple vaccination* against *diphtheria, tetanus* and *polio* at the age of five months he became restless, slept more badly as time went on and finally suffered from cramps. The diagnosis was: salaam seizure (a form of epilepsy), hypsarrhythmia (a very pathological EEG) with the prognosis of remaining physically and mentally handicapped. Through the chronic amnesia I learnt that Nick from the start had showed the picture of a sycotic infant, with flatulence colics, diaper dermatitis, conjunctivitis, difficulties to fall asleep and so on. His mother, too, showed clear signs of the sycotic miasm, for instance infant rheumatism, menstruation problems, candida infection in the genital area, a miscarriage, for a long time during childhood flatulence colics, inexplicable panic fears etc. The application of Medorrhinum LM18 – one drop in a spoonful of water every third day in the evening – afforded the boy a quite wonderful development. After an initial worsening of the cramps and an additional appearance of rashes on the head and in the face (like milk crust, neurodermatitis and psoriasis), but generally a mental and emotional maturation, the cramps and the other ailments disappeared, so that now Nick showed no abnormal symptoms whatsoever and started to develop normally.

In the chronic amnesia a homeopath will always inquire about inoculations. He is especially interested to know how many vaccinations had been administered during what length of time and how they were tolerated. The smallest disturbances that sometimes are observed after a vaccination, i. e. twitching of arms and legs, but also conspicuous signs like perpetual sleepiness, lack of interest, shrieking, an obvious break in development and more are very important factors. But not just overreactions point to a possible reaction to the vaccines. Even the absence of any reaction – like a lack of inflammation with smallpox, which then is followed by repeating the vaccinations – can be regarded as an indicator for the selection of the remedy. Especially the non-fight against a vaccine – when locally none of the usual signs appear by which the body frees itself from the injected toxins – is nevertheless a deep intrusion into the constitution; the "fight" becomes a chronic process, the so-called chronic vaccinosis.

CHILDHOOD DISEASES – A MIASMIC ATTEMPT AT SELF-HEALING

If a child is taken ill with a children's disease, this should be seen as the positive attempt by nature to free the body of one of these inherited miasms at least for some time – maybe five or ten years – (*syphilitic:* scarlet fever, diphtheria; *tuberculous:* whooping cough, measles, German measles; *sycotic:* mumps, varicella). *John Henry Allen* describes this very succinctly in his book *"The Chronic Miasms"*: *"If they (i. e. the childrens's diseases) are properly treated with the homeopathic remedies, they disappear without any follow-up diseases, whereby the complete system is largely freed from the present miasms and is renewed. But if the diseases have been treated wrongly, many types af chronic miasmic blockages (i. e. complicatians) may appear which either stay forevcr or slowly but surely ruin that person's life."*

Thus we may understand better that not every child goes through every children's disease. The organism needs the disease in question for its development, and not just on the organic level! Many parents may have noticed that after passing through a children's disease their child is not only physically more stable, but also mentally matured and more sensible. With every children's disease a maturation takes place that is important for human development. But this is only so when the disease is "left alone" and is not suppressed by fever-reducing medication, antibiotics, cortisone or other suppressants. Such measures massively hinder the body's discharging functions comparable to the suppression of the vagotonic healing phase and enhancing the risk of complications. To state it once more in all clarity: It is not the children's disease which causes possible complications, it is the predisposition, the inherited background, the miasm – *the disease behind the disease*, so to speak!

If going through one of the childhood diseases necessary for the organism is hindered by a conventional vaccination, there is no further possibility anymore to free oneself of the miasm active at that time. Usually a hardly detectable process is thus started that often tends to become chronic. This means that the organism has to a large degree been robbed of its individual regulatory potential! Childhood diseases are also displaced into adult life which is irresponsible, since they often are accompanied by complications.

The American female virologist *Hartmann*, a specialist for *German measles* and the vaccinations against it, found in those not inoculated against German measles a recurrence of the disease of only 3 %. In those inoculated however the quota rose to about 80 %! Despite having

been inoculated more than half of the children got the disease anyway! Thus the German measles vaccine does not protect against the danger of a recurrence during pregnancy and thus also not against the danger of damage to the unborn child (embryopathy from German measles), Mrs. Hartmann suggests: "The opportunity to go through German measles in childhood should be left to as many young girls as possible."

VACCINATIONS SEEN STATISTICALLY

Statistics of all infectious diseases over the last 150 years – also of those diseases against which no vaccination campaigns had been instigated, like cholera and scarlet fever – and the characteristic curves derived therefrom clearly show the continuous drop of epidemic diseases. This general drop, however, is not caused by the introduction of vaccinations, as is repeatedly contended, but by the hygienic-technical improvements civilization has brought to the general situation of the populace. The vaccinations that started only much later provoked a significant reduction of this welcome trend. From the start of mass vaccinations all curves, and this is highlighted again and again by serious specialists like *Buchwald* and *Delarue*, show a deterioration of the course of the epidemics. That means that after mass vaccination programs were begun the drop in the number of those newly infected by the disease concerned was slowed or the curve even began to rise again! Vaccinations were then brought in when there was a natural slump in infectious diseases, and after their introduction the influences that became apparent were more of a negative nature.

PROTECTION THROUGH VACCINATION – A MISLEADING PSEUDO-CONCEPT

Apart from these considerations there is no longer any doubt as far as many independent vaccination researchers are concerned that inoculation does not protect against the illness which it is supposed to prevent. If infection occurs despite the inoculation the illness frequently proves to be much graver and there is a higher risk of damage to the brain or other organs. Vaccination then can never be equalled to taking ill and recovering from an illness. Neither life-long immunity is achieved nor is any maturing process evident. The possibility of contracting the disease is not prevented, either, which is shown by the illnesses despite vaccination.

In addition immunologists disagree nowadays about what role the so-called antibodies really play in immunology. Orthodox medicine supports the premise that immunity is given as soon as antibodies are present; the hypothesis is then conceived with purely materialistic factors, based on a very simplified understanding of our immune system. It has, however, often been observed that people with a high antibody concentration in their blood died of the illness and others, who had no such antibody counts, survived or in fact never became ill at all, people that is who were expected to show some kind of pathological reaction at least. This picture includes exceptionally contagious diseases such as cholera. In the corpses of many persons who died of cholera there was no trace of vibrios to be found, whereas healthy persons carried the bacteria. *Max von Pettenkofer*, the world famous Professor for Hygiene, recognized this (he had made Munich the healthiest town in Germany by setting up sanitary installations), he snatched a retort with a pure culture of cholera bacteria that would have sufficed to spread the

disease to a whole regiment from the hands of *Robert Koch*, and swallowed the complete contents in front of his astonished colleague: "What counts is the organism. If your theory were right, I would be a dead man within 24 hours", he said.

The search for material substances is thus insufficient. The latest findings suggest that antibodies play a minimal role. They tell us that antibodies are only an accompanying factor of an extremely complex immunological reaction and at best represent the last link in a chain of defensive mechanisms, and can rarely be produced by persons in a healthy state. Our immune system is therefore much more complex than we have so far presumed. To reduce it to the mere presence of antibodies in such or such a concentration has proved to be an oversimplification and has moreover proved to be fallacious.

This incomplete hypothesis taught by immunologists becomes strikingly obvious in the case of vaccinations against *tuberculosis, tetanus* and *HIB (Haemophilus-influenzae-B)* since these three illnesses leave no kind of natural immunity. How should immunity be achieved through vaccination if it is not even given by a natural infection, and vaccinations try to work on the principle of copying nature?

The *antigene-antibody theory* (in the sense of the strongest sector of the immune defense mechanism) is not even conclusive and tenable according to orthodox medical tenets, or rather it never was or has been! Pasteur had willfully "deceived" the public in his day and committed scientific forgery by enhancing the results of his studies that had in reality delivered less convincing evidence. It was not until 1993 – after almost 20 years of studying Pasteur's private notes from his laboratory work (about 10.000 pages) that this fraud could be discovered by Dr. Gerald L. Geison of the Historical Institute of the University of Princeton (U.S.A.).

POTENTIAL DANGERS FROM THE VACCINES THEMSELVES

The bases of the individual vaccines are – depending on the disease concerned – quite different in nature. There are:

- so-called live vaccines with pathogens that can multiply both virus and bacteria based (e. g. measles, mumps, polio/oral vaccine after Sabin, German measles, tuberculosis, typhoid)
- inactivated viral vaccines (e. g. polio/injected vaccine after Salk, influenza, hepatitis-B, rabies)
- inactivated bacterial vaccines (e. g. whooping cough)
- toxin or toxoid vaccines (e. g. diphtheria, tetanus).

Since viruses can only exist and multiply in living systems they are usually cultivated in animals – in cell cultures and in fertilized hen's eggs – or extracted from the blood of infected animals. Examples of cultivating media are brain tissue of rabbits, renal tissue of dogs, rabbits and monkeys, protein from hen's or duck's eggs, chicken embryos, bovine serum, horse or pig blood and pus fram cowpocks: note that these are always live animals. Yet in an animal body, respectively in its organs, there also exist viruses that are able to react in a foreign organism quite differently than they would in the host organism from which they come. The effects such alien viruses may have on humans are largely unknown.

Cell cultures upon which viruses are cultivated may thus be contaminated by other (possibly totally unknown and not yet discovered) viruses that in this way might find their way into the vaccine. The attacking viruses are not inevitably rendered ineffective and thus may exist both in vaccines made from live and from inactivated viruses. One can never safely say that a cell culture is totally free of contamination by other viruses, for a substance can only be detected when the methods necessary for this detection are known. The theoretical possibilities are practically infinite, and one has to agree that any inoculation with live or inactivated viruses poses a potential risk. In virology the most re cent experiences led to the insight that viruses may exist today about which nothing is yet known and which cannot at present be detected.

For some time now many vaccines have contained additives that are known to be dangerous and to have a whole gamut of side effects. Antibiotics are added for instance to dampen eventual immune reactions or overreactions. This is rather irresponsible since the tendency of antibiotics to inactivate the immune response that the inoculated person especially needs is well known.

Also, vaccines contain a series of so-called stabilizers, neutralizers, carrier substances and preservatives, all of which we would never willingly ingest in our food. Among them we find formaldehyde, mercury, aluminium sulfate, acetone (a solvent) and phenol (caustic and very poisonous).

For some years now, human fetal cells (foreign human protein!), so-called MRC-5-cells[1] as well as human WI-38-lung-cells (Wistar Institute-38, Philadelphia, USA), have also been found in vaccines.

Further the "vaccine cocktails" land mostly directly in the bloodstream of the organism, which is unnatural. By-passing all physical defense barriers – skin, mucous membranes, tonsils, gastrointestinal tract, liver – these foreign proteins and neurotoxins are injected directly into the muscles (and thus into the blood)! Such intrusions are not programmed in Nature, since they simply do not occur! This must result in the organism being simply overtaxed. This "going against Nature" culminates in the U.S. in the doctors administering the oral polio vaccine also handing out the macabre advice not to recommence immediately in breastfeeding the baby since the mother's milk would contain neutralizing substances which would inactivate the polio virus in the intestine of the infant being breast-fed. And lastly, the vaccines – apart from the way they are produced – are tested in the most gruesome way in animal tests (as are almost all other drugs, too!), but here I will not go into this subject more deeply. I would just like to mention that the term "animal testing" feigns harmlessness and is a misnomer.

[1] MRC-5 (Medical Research Council cell strain 5) is a diploid human cell culture line consisting of fibroblastic cells from the lungs of a 14-week-old male fetus. The fetus was aborted in September 1966 by a 27-year-old, otherwise physically healthy mother due to psychological problems. These MRC-5 cells show a low frequency of chromo-somalic abnormalities.

VACCINATION OF ANIMALS

If according to the natural laws presented vaccinations make no sense, this also has to be valid for animals. Here, too, we should observe that vaccinations do not protect but harm, and this is exactly so. In Germany since 1992 vaccinations against *foot-and-mouth disease* have no longer been allowed. Even importing inoculated animals or animal products from countries where the vaccination is still being undertaken is prohibited. In the revised version of the *German animal pest law* that had come into force half a year before, this vaccination is in fact no longer mentioned.

The decision to go along with the EU recommendation and lift the enforcement of vaccination, which means stopping vaccination against foot-and-mouth disease outright, is but the logical conclusion that should also have been applied to us humans a long time ago. The data of 1966 to 1988, during which period countries with and without yearly mass vaccinations coexisted. clearly show that in the countries with enforced vaccinations there were considerably more outbreaks than in those countries without legal stipulations to regulate vaccinations. The inoculating countries were always the starting points of open epidemics and thus actually a danger for the countries free of the disease. In the non-inoculating countries it was definitively proved that the disease only appeared through being brought in or transmitted from neighbouring inoculating counntries.

Similar observations were made by African preservationists in 1989 about the African wild dog (hyena dog) that at the moment is severely threatened with extinction. After scientists had marked individual animals in the course of their research and had inoculated them against *rabies*, more than a dozen packs died within one year from rabies as tests showed. And this even in areas where the disease had never been observed before! The researchers who in the beginning only had inoculated individual dogs decided after their demise to vaccinate the dogs of the remaining packs with a non-infectious form of the pathogen. In this way they wanted to prevent the sudden death of the remaining animals. But the exact opposite happened: all members of the seven packs inoculated disappeared within the following year. Against this background the Swiss practice to lure and in this way inoculate wild foxes with chicken heads laced with a rabies vaccine seems rather questionable. The exact opposite to the eradication of this dreadful infectious disease is thus perpetrated, namely its spreading! Similarly for domestic animals. To my knowledge a rabies shot is obligatory for every new dog license – and this every two years. A great danger also to the owners, especially for their children, for what child will not cuddle its beloved four-legged friend?

Another example concerns our saddle-horses. Their “immune system is also ruined slowly and surely by a multitude of vaccinations” (spoken by a vet). In most stables routine vaccinations and worm treatments must be attested, which frequently leads to acute and/or chronic ailments (cough, influenza, frequent bouts of illness, weakness, aggressivity, paralysis, inflammation of tendons, even miscarriages or stillbirths with pregnant mares, with young foals symptoms just as we find in sycotic babies in the form of diaper dermatitis. including diarrhea, sore and in some cases weeping wounds of the hindquarters as well as loss of hair in that region, and so on.

The opinion of an American female vet on this topic tells the whole story: “For a homeopath it is virtually impossible to heal an animal without first tackling the problems that the animal

has suffered through vaccinations, whatever species of animal is concerned." Another vet stated quite drastically at a vocational training congress of homeopathic vets in Germany (after he had made sure that all recording devices were switched off): "We are vaccinating the animals 'to death' and most of our colleagues know that." Even Pasteur had to pay compensation to owners of flocks for those animals that died because of his vaccinations (anthrax). Moreover the fact that all cattle reared for meat – apart from a very few – are regularly vaccinated should be taken into consideratian by all consumers of meat and sausage. Few people are aware of the situation where most meat has not only a hormone content but is also affected by several different vaccinations.

"HOMEOPATHY MAKES VACCINATION SUPERFLUOUS"

From homeopathic practice we know that reactions to and damage from vaccination occur especially when chronic diseases are prevalent within the family. So it is always a question of the personal history! A thorough homeopathic anti-miasmic therapy with the aim of cleaning the terrain therefore seems to be the best protection. If possible this should be done with the future parents before conception. If this is no longer possible, during pregnancy is a good time to effect a lot for the future mother, but also for the health of the child to be born, for "during pregnancy the miasm speaks very distinctly".

On the whole ane can observe that people who by now are being homeopathically treated in the second or third generation rarely suffer from acute illnesses, and if they do, it is intense, but only of short duration and without complications – and therein lies our greatest chance.

A pediatrician well known in homeopathic circles states unequivocally: *"Homeopathy is a form of therapy that renders vaccinations redundant, for it heals the weaknesses (i. e. the miasms) which form the basis for infectious diseases and their complications."*
For this reason we should not try to disregard the problematic nature of vaccinations as a whole, or try to treat it playfully and bring it down to a "jab", because not only the conventional conception of vaccinations is extremely questionable, but they cannot offer any real form of protection whatsoever, and moreover, according to the personal medical history and within the family, they can prove to be quite dangerous.

To put it in a nutshell: *Vaccinations are a gross disregard of the laws of Nature!!*

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See also the essay/article "Severe Vaccination Damage and its Homeopathic Cure":
www.tisani-verlag.de/VaccinationDamage_e.pdf

Dr. Joachim-F. Grätz is an internationally recognized homeopath, very well known in German-speaking areas. He has written several books about Classical Homeopathy including the chronic miasms, vaccination damages and their homeopathic cure as well as about 100 essays/articles in magazines and homeopathic journals.

See also Dr. Joachim-F. Grätz's two DVDs:
„Impffrei – Ein Grundstein für «chronische» Gesundheit"
("Vaccine-free – A cornerstone for «chronic» health")
www.tisani-verlag.de/dvd

Questionnaires for homeopathic therapists as well as parents:

- *Questionnaire for Your Homeopathic Anti-Miasmatic Treatment:*
  www.tisani-verlag.de/html/englishqfragebogen.html
- *Questionnaire for the Homeopathic Treatment of Your Child:*
  www.tisani-verlag.de/html/englishqfragebogen1.html

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VACCINE CRISIS COMMUNICATION MANUAL

A STEP-BY-STEP GUIDANCE FOR NATIONAL IMMUNIZATION PROGRAMMES

ABSTRACT

This manual was developed to support countries in effectively responding to events which may erode the public's trust in vaccines and the authorities that deliver them. In addition, a small section of this manual focuses on how to best prepare for a potential crisis and provides some insights into conducting post-crisis assessments. For the response phase, step-by-step guidance is provided on how to manage the communication aspects of a vaccine crisis.

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World Health Organization
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VACCINE CRISIS COMMUNICATION MANUAL

A STEP-BY-STEP GUIDANCE FOR NATIONAL IMMUNIZATION PROGRAMMES

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This manual was developed based on WHO Regional Office for Europe:

- guidance on vaccine safety and crisis communication,
- in-country training sessions on vaccine safety communication and new vaccine introduction, and
- desktop research in the field of crisis, risk and emergency communication.

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ABBREVIATIONS

AEFI	adverse event following immunization
HPV	human papillomavirus
NGO	nongovernmental organization
SIDS	sudden infant death syndrome
UNICEF	United Nations Children's Fund

GLOSSARY

ADVERSE EVENT FOLLOWING IMMUNIZATION *(1)*	Any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable sign, abnormal laboratory finding, symptom or disease.
VACCINE CRISIS COORDINATION MECHANISM	A coordination mechanism established by the ministry of health or other health authority to prepare for and respond to a vaccine crisis This is normally a vaccine crisis coordination group consisting of stakeholders from various institutions representing different areas of expertise, including immunization experts and communication experts. In a crisis, this group can be restructured or expanded to include relevant experts as appropriate for the context (e.g. a human papillomavirus (HPV) vaccine-related crisis will require a different set of stakeholders to respond than a crisis related to the publication of a negative article). The group may have a subgroup focused specifically on communication and it should develop a vaccine crisis communication plan.
VACCINE CRISIS	This manual defines a vaccine crisis as an event which will most likely or has already eroded public trust in vaccines and/or vaccination and the authorities delivering them and may create uncertainty. This requires immediate action and an effective response to curb the negative impact Vaccine-related events may or may not be directly caused by vaccines/vaccination itself.
VACCINE-RELATED EVENT	A vaccine-related event is any event which could potentially create uncertainty and/or erode the public's trust in vaccines and/or vaccination and the authorities delivering them. Not all vaccine-related events will develop into a crisis. Vaccine-related events may or may not be directly caused by vaccines/vaccination itself.

INTRODUCTION

Every immunization programme eventually faces events that have the potential to erode trust in vaccines and/or vaccination and the authorities delivering them.

This could be a change in the routine immunization schedule, the introduction of a new vaccine, a false rumour related to a vaccine, or any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. In this manual we refer to these collectively as "vaccine-related events".

For immunization programmes, it is crucial to be well prepared and have a mechanism in place to respond to vaccine-related events, which may, at any time, evolve into crisis situations.

This document provides immunization programmes and other stakeholders with step-by-step guidance on how to effectively manage the communication response to vaccine-related events, particularly those with a potentially high impact on public trust, which are therefore considered to be a vaccine crisis.

Countries are encouraged to use this manual as inspiration to create their own, country- and context-specific vaccine crisis communication plans.

While there are three general phases of vaccine crisis management, this manual mainly focuses on communications actions related to the response phase.

However, to provide the broader context, it also offers suggestions for assessing the communication response to vaccine-related events that may not develop into a crisis, and a short section on communication actions during the preparedness and post-crisis evaluation phases (Fig. 1).

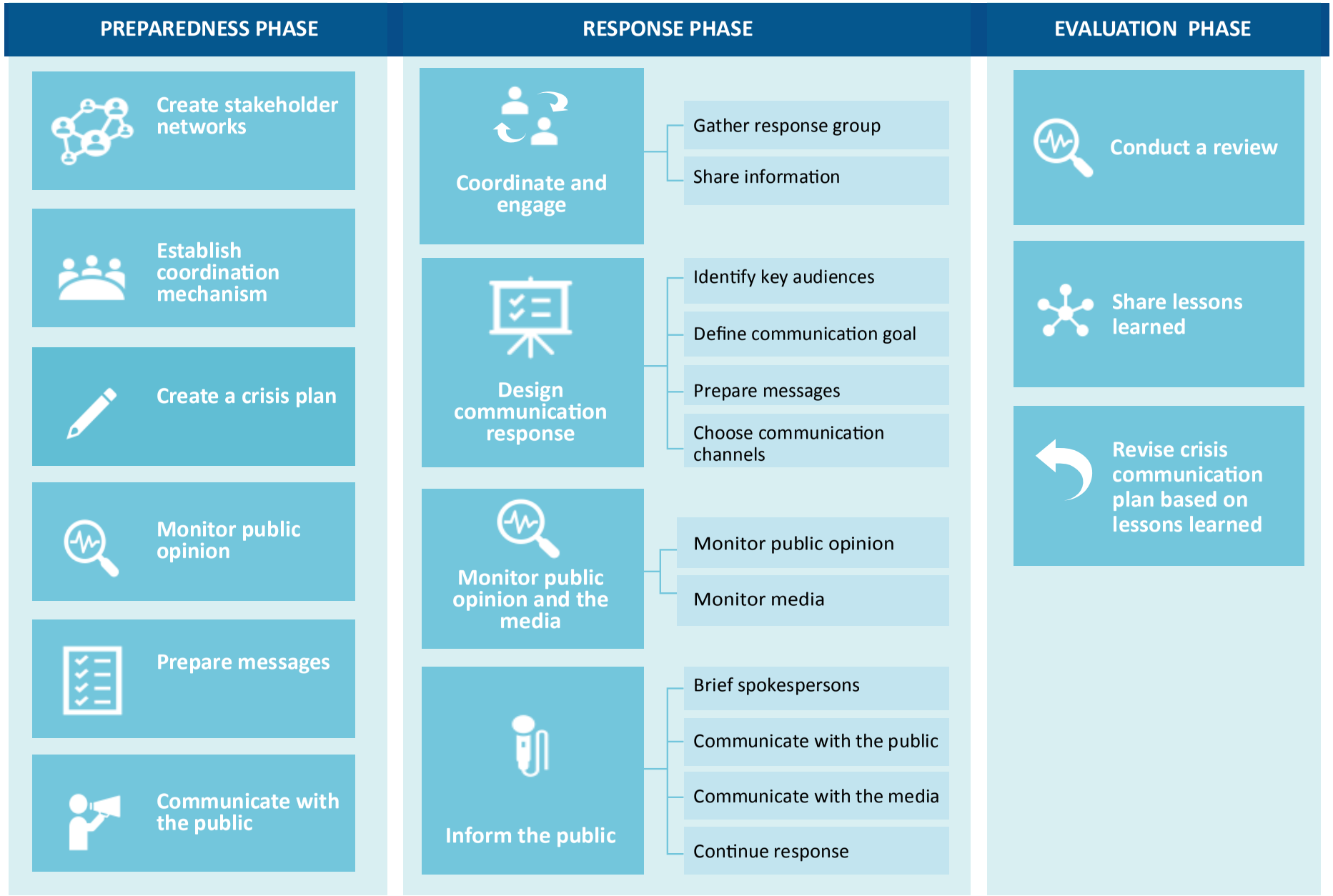
The manual draws on the WHO Regional Office for Europe Vaccine safety communication library. *(2)* Throughout the manual, references are made to documents in the online library for further information and guidance. When communicating about and during a so-called "vaccine crisis" (see definition in "Glossary" page iv), the main goal is to rebuild trust in vaccines as one of the most important public health interventions.

As crisis management is an iterative and rapidly evolving process, the order of suggested actions may vary in practice.

Each crisis differs and thus requires a tailored, country-specific response.

COMMUNICATION-RELATED ACTIONS IN EACH PHASE OF VACCINE CRISIS MANAGEMENT

Fig. 1. Communication-related actions in each phase of vaccine crisis management



Source: Based on the Vaccine safety communication library and established principles of risk communication.

INTRODUCTION > WHO IS THIS MANUAL INTENDED FOR?

This manual serves as overall guidance to immunization programmes and other stakeholders. National authorities are encouraged to use this document as a basis for developing a country-specific vaccine crisis communication plan, thus strengthening national immunization systems' capacities to respond to any vaccine-related event.

While this manual aims to support national immunization programmes, it may benefit all stakeholders directly involved in communications as part of vaccine crisis management, including:

- immunization programme staff;
- ministries of health and education, and other relevant ministries;
- institutes of public health;
- public health institutions and associations;
- others working in the field of immunization, both at national and subnational levels;
- other partners (e.g. United Nations organizations, nongovernmental organizations (NGOs), civil society organizations).

Stakeholders involved in vaccine crisis management may vary from country to country and depend on the context of each crisis. For example, crises related to human papillomavirus (HPV) vaccination may involve a broader range of stakeholders, including organizations working in the field of cancer and women's health.

INTRODUCTION > CRISIS RESPONSE AT ONE GLANCE – CHECKLIST

ACTION	COMMENT	STATUS
COORDINATE AND ENGAGE		
GATHER RESPONSE GROUP	Gather vaccine crisis coordination group formed in the preparedness phase and activate the vaccine crisis communication plan.	☐ Not started ☐ In Progress ☐ Completed
SHARE INFORMATION	Make sure to establish a coordination modality and regularly share and exchange information.	☐ Not started ☐ In Progress ☐ Completed
DESIGN COMMUNICATION RESPONSE		
IDENTIFY KEY AUDIENCES	Conduct a quick assessment to identify key audiences. Successful communication depends on how well messages are tailored to the needs of specific audiences.	☐ Not started ☐ In Progress ☐ Completed
DEFINE COMMUNICATION GOAL	Define the overarching communication goal and related targets. These will guide your communication response and accompany you throughout the crisis.	☐ Not started ☐ In Progress ☐ Completed
PREPARE MESSAGES	Based on your audience analysis, prepare messages, which can be easily adapted to the evolving nature of the crisis and related needs of different population groups.	☐ Not started ☐ In Progress ☐ Completed
CHOOSE COMMUNICATION CHANNELS	As a next step, choose adequate communication channels, through which you will best reach your target audiences.	☐ Not started ☐ In Progress ☐ Completed
MONITOR PUBLIC OPINION AND THE MEDIA		
MONITOR PUBLIC OPINION	Understand the public's concerns and needs is crucial. Use existing or implement new monitoring tools to monitor public opinion. This will help you better address their needs through tailored communication.	☐ Not started ☐ In Progress ☐ Completed
MONITOR MEDIA	Monitor what the media reports about the crisis. Good relations with key journalists and the media will help you in times of a crisis.	☐ Not started ☐ In Progress ☐ Completed
INFORM THE PUBLIC		
BRIEF SPOKESPERSON	Make sure chosen spokespersons are trusted by the audiences you wish to address. Ideally, the spokesperson(s) chosen has had some training in vaccine crisis communication.	☐ Not started ☐ In Progress ☐ Completed
COMMUNICATE WITH THE PUBLIC	Communicate regularly with the public. Even in times of uncertainty, make sure to convey the six trust-building mechanism: professionalism, objectivity, empathy, sincerity, competence and consistency. *(3)*	☐ Not started ☐ In Progress ☐ Completed
COMMUNICATE WITH THE MEDIA	Communicate regularly with the media. Preparing talking points and circulating them among members of the coordination group helps align messages and maintain trust.	☐ Not started ☐ In Progress ☐ Completed

The main goal of the preparedness phase is to conduct ongoing communication activities to maintain and build public trust in vaccines, vaccination and the authorities delivering them. It is crucial to be well prepared for events which may erode trust in vaccination.

The preparation phase does not represent an ad-hoc event, but rather an ongoing process of maintaining relations with all relevant stakeholders, keeping the public informed to build resilience against misinformation, monitoring public opinion and regularly updating, or if not yet available establishing, a coordination mechanism and national vaccine crisis communications plans.

Populations that are well informed about vaccination are less likely to be affected by vaccine scares, misinformation and rumours. Table 1 outlines key actions which may be considered in the preparedness phase.

Table 1. Preparedness phase – key actions

KEY ACTION	RECOMMENDATION	AVAILABLE GUIDANCE DOCUMENTS
CREATE STRONG STAKEHOLDER NETWORKS	Identifying key stakeholders and building strong relations are critical in effectively communicating about vaccination in general. Particularly in a crisis, strong networks will help you align your crisis response and mitigate negative effects on public trust more easily and in a more coordinated manner. Stakeholders can be strong advocates and may have knowledge of and access to key population groups. Remember: build strong relationships before a crisis occurs. A crisis is not the ideal time to start establishing new relations.	**WHO Regional Office for Europe** Stakeholder management *(4)*
ESTABLISH COORDINATION MECHANISM	Establish a coordination mechanism (normally a vaccine crisis coordination group) including a communication component and create a vaccine crisis communication plan. This will allow you to build working and collaborative relations with your partners and colleagues, to strengthen ongoing communication for immunization and to ensure a well-coordinated response based on aligned messages. Make sure to meet on a regular basis, also when there is no crisis. Suggested members: representatives of the ministry of health (all levels), public health institute, public health institutions and associations, ministry of education, national regulatory authorities, research organizations, international organizations, civil society organizations and professional organizations, and other relevant stakeholders, such as journalists and communication experts.	**WHO Regional Office for Europe** Template terms of reference for a vaccine communication working group *(5)*
CREATE A CRISIS PLAN	Create a vaccine crisis plan focusing on communication preparedness and response. Seek input from members of the coordination mechanism created in the previous stage. This will help form alliances and make sure all partners and key stakeholders are on the same page.	
MONITOR PUBLIC OPINION	To monitor trends, identify a potential crisis before it evolves, and develop evidence-informed tailored communication materials and activities, it is crucial to conduct social listening to better understand the public's concerns, beliefs, attitudes and practices toward vaccination. This can be conducted through social media monitoring, surveys and qualitative/quantitative research studies. Keeping track of public opinion and misinformation	**WHO Regional Office for Europe** Four critical elements in the ongoing work to build and maintain confidence *(6)*

KEY ACTION	RECOMMENDATION	AVAILABLE GUIDANCE DOCUMENTS
PREPARE MESSAGES	When introducing a new vaccine prepare some key messages in advance (although this may not be possible for unforseen AEFIs). For example, when introducing the HPV vaccine, key messages can be prepared on the safety profile of the vaccine, HPV-related viruses and diseases, and common concerns raised (e.g. on fertility and HPV vaccination). It is recommended to conduct formative research prior to the introduction of any new vaccine to inform health authorities about existing beliefs, concerns and misperceptions concerning the new vaccine and the disease the vaccine was designed to protect against (e.g. cervical cancer). Based on the results and the specific need for information, tailored key messages can be prepared and disseminated to key audiences. If time allows, messages should be pre-tested to ensure that information shared will be received in the way it is intended. Based on the pre-testing, messages can then be revised accordingly to better reach target audiences. Main principles for preparing messages: **BE ACCURATE.** Cite facts, evidence and data. **BE HONEST.** Do not try to conceal facts. **BE SIMPLE.** Use clear, non-technical language and no acronyms. When using technical language, be sure it matches the target audience's level of understanding. **EMPHASIZE** the value of immunization based on a risk-benefit analysis.	**WHO Regional Office for Europe** New vaccine introduction – Checklist for planning communication and advocacy *(7)* A field guide to qualitative research for new vaccine introduction *(8)*
COMMUNICATE WITH THE PUBLIC	To establish and maintain trust in vaccines and the authorities delivering them, it is crucial to engage in regular dialogue with the population. Bi-directional communication on trusted channels and platforms (e.g. social media, television interviews, print media) is an important trust-building mechanism.	**WHO Regional Office for Europe** Responding to concerns about vaccination *(9)* Best practice guidance: How to respond to vocal vaccine deniers in public *(10)*. Lewandowski et al. The COVID-19 Vaccine Communication Handbook **United Nations Children's Fund (UNICEF)** Interpersonal communication for immunization. Training for front line workers *(11)* Sharing Knowledge About Immunization Talking about immunisation *(12)* **Centers for Disease Control and Prevention** Toolkit for Reaching Parents and Patients *(13)* Talking to parents about vaccines *(14)* **European Centre for Disease Prevention and Control (ECDC)** Communication on immunisation *(15)*

When preparing to respond to an event, it is crucial to assess the situation carefully in order to strike a balance: communication must be transparent, complete and timely if the situation involves a potential threat to public health, but it should not amplify a minor event or draw attention to false claims that could raise unnecessary concerns.

This manual proposes a three-step model to guide readers in assessing the situation and defining the response. It should be highlighted that every situation is different and requires a tailored response adapted to the context of the situation, as well as target audience and country setting.

Assess the type of vaccine-related event

Vaccine-related events that may evolve into a crisis can be clustered into three categories: AEFI, change in the immunization system or schedule, or negative public or media debate/publication (Fig. 3).

Fig. 3. Types of vaccine-related events

ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI) which are (rightly or wrongly) being associated with vaccines or vaccination and may create uncertainty or distrust among the public

Example: sudden infant death syndrome (SIDS) following immunization

CHANGES IN THE IMMUNIZATION SYSTEM OR SCHEDULE which may create uncertainty among the public

Examples: introduction of a new vaccine, mass vaccination campaigns, suspension of a vaccine or temporary recall of a vaccine

NEGATIVE PUBLIC AND MEDIA DEBATE/ PUBLICATION on vaccination which may create uncertainty and distrust among the public

Examples: new critical scientific studies, social media stories or critical media reports

Note: This figure does not represent an exhaustive list of events. Other events related to vaccination and/or the immunization programme may also have the potential to develop into a crisis.

Source: Adapted from guidance documents which are part of the Vaccine safety communication library, in particular How to ensure a context-specific response to events that may erode trust. *(16)*

Some events can be foreseen, or are even planned, and others may appear on an ad-hoc basis. While a new vaccine introduction or a change to the immunization schedule represent planned actions based on a decision-making process, AEFIs or a baseless accusation made by a powerful anti-vaccination group can suddenly gain widespread attention. Such different events require different responses.

Gather information

Consider the five Ws: who, what, when, where and why, as outlined in Table 2.

Table 2. Gathering information to understand the event

FIND ANSWERS TO THE FOLLOWING QUESTIONS:

What happened? How serious is it?

Who is involved?

Who could influence the impact? Think about active and passive influencers.

Which vaccine is being (rightly or wrongly) linked to the event?

What may be the cause of the event?

Where and when did it happen?

BE FAMILIAR WITH YOUR COUNTRY'S CONTEXT:

Immunization coverage rates (any increase/decrease noted)

Possible debates on vaccine safety in media/social media

POTENTIAL SOURCES OF INFORMATION:

AEFI monitoring reporting system

Experts from the ministry of health and the public health institute

Local health workers

Laboratory, monitoring, surveillance, procurement and logistics staff (depending on the type of event)

National regulatory authority

Other relevant ministries (e.g. ministry of education)

Immunization experts and advisers

Assess potential impact

Assess whether the event has the potential to have a **LOW**, **MEDIUM** or **HIGH** impact on trust.

LOW POTENTIAL IMPACT

EXAMPLES: The vaccine is replaced with only a slightly reconfigured product; events with no public attention nor (social) media coverage.

COMMUNICATION-RELATED ACTIVITIES: Maintain effective communication to ensure public trust in immunization; engage in routine communication; keep a close eye on the public debate.

MEDIUM POTENTIAL IMPACT

EXAMPLES: An event in another country (such as change of schedule) with a vaccine used in your country; the event gets no media attention at this stage, but media attention could be anticipated; minor AEFI or with unlikely link to vaccination with media coverage restricted to one local area; false claim made by a popular social media influencer that begins circulating in the country. It is important to mention that medium impact events may develop into high impact events, if the situation changes or the response is not managed adequately and in time.

COMMUNICATION-RELATED ACTIVITIES:

Prepare for a potential public debate on the topic.

Start developing messages; share them with key stakeholders, spokespersons and partners (e.g. who may be contacted by the media or public).

Where appropriate, start communicating with selected audiences, but not yet to a wider audience.

Activate your stakeholder network.

Continue to monitor and gather information about the event and public opinion.

HIGH POTENTIAL IMPACT

EXAMPLES: Death following vaccination (pending investigation); cluster of minor AEFIs; events which involve children, the elderly, pregnant women or vulnerable groups; the introduction of a new vaccine; vaccine recall; vaccine suspension, mass vaccination campaign; misleading but powerful story/publication which attracts a lot of negative (social) media attention.

RESPOND IMMEDIATELY: Follow the steps outlined in Phase 2: Crisis response.

Specific case examples for each category of event are outlined in Annex 1.

Fig. 4 illustrates different communication strategies depending on the impact the event may have on the public's trust in immunization and the authorities delivering them. For more information, consult How to ensure a context-specific response to events that may erode trust *(16)*.

Fig. 4. Communication strategies based on impact assessment

LOW IMPACT	MEDIUM IMPACT	HIGH IMPACT
CONTINUE WITH ROUTINE COMMUNICATION. BE PREPARED! => PHASE 1: PREPAREDNESS	DO NOT COMMUNICATE WITH THE PUBLIC YET. => INTENSIFY PREPAREDNESS EFFORT AND BE READY TO PROCEED TO CRISIS RESPONSE.	RESPOND IMMEDIATELY! => PROCEED TO PHASE 2: CRISIS RESPONSE.

CRISIS RESPONSE

The following actions are intended for events classified as having a potentially **high impact on public trust**. Actions outlined in this chapter may also be considered for **medium-impact** events, which may develop into a full-scale crisis.

Your response during the initial hours and days of a vaccine crisis will help determine the further development and outcome of the crisis. Follow the action points in the response phase (Fig. 5) to successfully manage the first few days of an actual crisis.

REMEMBER! In the initial response phase, transparent internal and external communication is already key. Even if information gathering is still ongoing, fully and accurately communicating what you already know demonstrates transparency and builds trust.

Fig. 5. Crisis response – key communication actions

COORDINATE AND ENGAGE	UNDERSTAND AND ASSESS THE EVENT	MONITOR PUBLIC OPINION AND THE MEDIA	INFORM THE PUBLIC
Gather response group	Gather information	Monitor public opinion	Prepare messages
Share information	Identify type of crisis	Monitor media	Brief spokespersons
	Identify key audiences		Inform public and media
	Define communication goals		Continue response

MAKE SURE
to include relevant stakeholders in defining a shared strategy

AGREE
on roles and responsibilities

Consult the following documents in the online library:

- How to ensure a context-specific response
- Vaccine safety messages (frequency AEFIs)
- Stakeholder management
- Tips for spokespersons
- Key principles for presenting data
- Safety events: the immediate media response
- Setting the media agenda
- Four immediate steps when responding
- How to monitor public opinion
- How to respond to concerns
- The questions journalists always ask in a crisis
- Strategies used by journalists

VACCINE SAFETY COMMUNICATION LIBRARY *(2)*

CRISIS RESPONSE > COORDINATE AND ENGAGE

Gather vaccine crisis coordination group

In a crisis, gather the vaccine crisis coordination group formed in the preparedness phase (see glossary) and activate the vaccine crisis communication plan.

It is crucial to gather all key stakeholders regularly and from the very onset of the crisis. Consider which method of information dissemination to the group can be applied within a few hours: email, messaging services, phone tree. If possible, meet face-to-face or online for a quick information and brainstorming session.

For further information consult the following documents:

- Stakeholder management *(4)*
- Four immediate steps when responding to an event that may erode trust *(17)*
- Template terms of reference for a vaccine communication working group *(5)*

VACCINE SAFETY COMMUNICATION LIBRARY *(2)*

Share information

Regularly sharing information with the crisis response group and other important stakeholders ensures that all parties work together to achieve common goals. Further, the mechanism of regularly sharing information either via email, phone, messenger service groups or in face-to-face or online meetings creates a two-way communication stream, which allows stakeholders to update each other. This way, they can respond with the same messages to the media, detect rumours and new developments faster, and disseminate messages faster among various key audiences.

CRISIS RESPONSE > DESIGN COMMUNICATION RESPONSE

Identify key audiences

Knowing who the key audiences are allows for messages
and actions to be tailored to the specific needs, concerns and fears of different population groups or stakeholders (Table 3).

At the onset of a vaccine crisis, public opinion on vaccination (or a specific vaccine) should be rapidly assessed (for more information see 2.3. Monitor public opinion and the media). To ensure that your messages reach the right audience, you can group target audiences into separate categories depending on their level of influence and how affected they may bee by the crisis (Table 3).

Consider audience characteristics:

- most affected/not affected
- at risk/not at risk
- easy/hard to reach
- in specific language, gender or age groups
- influenced by cultural or religious norms
- knowledgeable/not knowledgeable
- in specific geographic location
- influencers/not influencers.

Table 3. Example of classification of key audiences

GROUP I:	GROUP II:	GROUP III:
MOST AFFECTED BY CRISIS	**ACTIVE INFLUENCERS**	**PASSIVE INFLUENCERS**
Populations most affected by a crisis. Who the key audiences are varies from crisis to crisis. As every crisis is different and needs a context-specific response, it is important to conduct an assessment to identify who the key audiences are and what their communication needs are. Example: parents whose child has suffered from an allergic reaction (anaphylaxis) to a vaccine component.	Those who directly influence the perceptions or behaviours of Group I. They help Group I to implement suggested behaviour change. These could include: • health-care workers (e.g. local general practitioners, vaccination nurses); • local leaders; • religious leaders; • opinion leaders; • local community and family members; • community-based organizations; • parents and grandparents; • teachers; • journalists, social media influencers; • immunization staff at district level.	Those whose actions indirectly help or hinder the perceptions or behaviours of Group I. Their reactions are embedded in the broader social, cultural and policy factors and can be used to create an enabling environment to sustain desired behaviour change. These could include: • academics; • influencers, such as popular health-care workers; • politicians; • policy-makers; • partners; • United Nations and other international organizations; • NGOs; • social mobilization teams; • civil society organizations; • bloggers; • those who oppose health authorities' views.

Define communication objectives and actions

Based on your knowledge of the event and key audiences, define communication objectives and determine actions to be taken (Table 4). The objectives should represent the desired behaviours you would like to maintain or achieve, and the actions determined to be taken should work towards bringing about that change.

Table 4. Example of communication objectives and actions

OBJECTIVES	ACTIONS
The main objective should be to sustain or restore trust of the general public in immunization as a lifesaving health intervention. Further objectives should be to motivate the public and/or achieve mutual understanding about issues that relate to vaccination and the immunization programme.	Actions should be focused on the audience. Define 2–6 actions that will support the achievement of your objectives. The actions should be tailored to the type of crisis and involve spreading evidence-based information about the facts surrounding the crisis.

EXAMPLE

An infant has died of sudden infant death syndrome (SIDS) within 24 hours after having been immunized at a local health centre. Preliminary evidence indicates no causal link between the death and the vaccine.

OBJECTIVE: to maintain (or restore) the public's trust in the administered vaccine and in the national immunization programme, including in health workers.

DETERMINE ACTIONS TO BE TAKEN: possible actions to be taken in this example might include the following:

communicate about the event and as soon as possible about the outcome of the preliminary investigation on causality assessment;

establish a 24-hour hotline to answer questions on vaccine safety and immunization.

engage community leaders;

engage with local media;

provide information on the overall immunization risk–benefit scale and the particular vaccine at local health posts and in community centres.

Prepare messages

Now prepare messages to address the specific event (Table 5). Preparing messages serves the purpose of being able to respond more efficiently and more quickly. It is crucial to share these with your network and key stakeholders to ensure that messages are aligned to avoid mixed messaging, so the public is reassured that authorities are managing the situation and communicating in a transparent way. See Table 6 for a concrete example of how to tailor messages to different target audiences.

Consider the following tips:

- Know which messages you would like to send to target audiences; and what you aim to achieve with the messages.
- Make sure to pre-test messages and revise accordingly to better reach target audiences.
- If an injury or death is involved, be sure to sincerely communicate your empathy to the affected families.
- Include as appropriate and based on the available evidence the risks and benefits associated with vaccination and vaccine-preventable diseases, the core message that the vaccine is safe and effective and should continue to be given to protect people from a given infectious disease.
- Messages should be short, concise and evidence based.
- Create a series of messages for each target audience and support your arguments with facts/evidence (refer to reputable sources).

Table 5. Possible messages related to various potentially high-impact events

WHEN YOU HAVE NO OR VERY LIMITED INFORMATION

Our deepest sympathy goes to those affected.

We are committing all available resources to the investigation of this unfortunate incident and are doing our utmost to find the cause as soon as possible.

We will keep you informed and provide regular information via our website www.xxxxx.zz and daily press briefings at the Ministry of Health.

WHEN MORE IS KNOWN ABOUT THE EVENT

Our deepest sympathy goes to those affected.

Vaccination saves lives and prevents suffering. The risk of severe side effects is extremely small. Some mild and more frequent side effects that may occur include a light rash and fever. The benefits of vaccination by far outweigh the minimal risk of a severe adverse event following immunization.

For example: 1 in 1 000 000 individuals vaccinated may suffer from a serious allergic reaction (anaphylaxis).

The vaccine is prequalified, which means it has been approved by WHO. Before prequalification it was rigorously tested through clinical and field procedures. After prequalification, WHO regularly inspects the production facilities to ensure compliance with good manufacturing practice.

Scientific evidence shows that combined vaccines save time and money through fewer clinic visits, reduce discomfort for the child through fewer injections and increase the probability that the child will receive the complete set of vaccinations according to the national schedule.

Despite high immunization coverage for [insert name of vaccine-preventable disease], some children are still missing out on vaccination and thus remain at risk.

Our country has taken all necessary steps to avoid a future outbreak of [insert name of vaccine-preventable disease] by initiating a [insert name of vaccine-preventable disease] vaccination catch-up campaign.

Table 6. Example of tailoring messages to different target audiences

SCENARIO: A GIRL WITH A SERIOUS UNDERLYING CONDITION HAS DIED FOLLOWING HPV VACCINATION Expressing condolences; stressing the fact that an investigation is ongoing; preliminary findings suggest that there is no causal relation between the death and the vaccine.	
TARGET AUDIENCE: GENERAL PUBLIC Multiple studies have proven the safety and effectiveness of the HPV vaccine in protecting young girls and women from a series of HPV-related cancers, including cervical cancer, which accounts for more than 30 000 deaths in the WHO European Region each year. Continuing vaccination efforts is thus crucial.	
TARGET AUDIENCE: HEALTH-CARE WORKERS Multiple studies, including Phase III randomized trials, have proven the safety and effectiveness of the HPV vaccine to prevent high-risk HPV infections and subsequent carcinogenesis. These studies have not shown any relation between the development of this underlying condition and the HPV vaccine.	
TARGET AUDIENCE: PARENTS AND CAREGIVERS Multiple studies have shown that the HPV vaccine is safe and effective, and has successfully been introduced in more than 100 countries worldwide. The HPV vaccine combined with regular screenings is the best, safest and most effective tool we have in protecting your daughters against HPV-related cancers.	
TARGET AUDIENCE: PEOPLE LIVING IN THE AFFECTED COMMUNITY It is important to continue vaccinating against HPV, as this is the most effective and safest tool we have in preventing HPV-related cancers, including cervical cancer, which kills more than 30 000 women in the European Region each year and can leave a woman without the possibility to bear children and have a family of her own.	

For more message examples consult the following document: How to prepare a message map *(18)*

Choose communication channels

In choosing adequate communication channels to communicate your messages (Table 7), think about which channels can best be used to reach your key audiences and thereby achieve your goal. Determine how key audiences receive health information and whom they rely on for health advice and guidance.

Table 7. Communication tools and channels

TOOLS	CHANNELS
• News releases, press conferences • Media interviews, commentaries and opinion pieces • Public services announcements • Brochures, banners, posters • Radio and television appearances • Informative web pages • Podcasts, blogs, vlogs, videos • Live Q&A • Chatbots, phone apps • Training courses, webinars, lectures • Hotline	• Traditional media (newspapers, television, radio, online news) • Social media • Community networks and meetings • Networks (parents, health workers etc.) • Partners (WHO, UNICEF, NGOs, local organizations, etc.) • Bloggers and social media influencers • Interpersonal (health workers, teachers, religious leaders, others) • Face-to-face meetings with the affected audiences (e.g. parents, health-care workers)

For further information consult the following documents:

- Four critical elements in the ongoing work to build and maintain confidence *(19)*
- How to prepare a message map *(18)*
- How to prepare a press release *(20)*
- Setting the media agenda *(21)*
- Safety events: planning the immediate media response *(22)*
- Effective communication of immunization data *(23)*

Monitor public opinion and the media

Monitoring public opinion about vaccines, vaccination, health authorities and other relevant topics before and during a crisis can help you respond more efficiently. Monitoring mechanisms, including social listening, should be ongoing and expanded as needed when a crisis hits. This will allow you to better understand what the population's thoughts, beliefs and concerns are and how they change during the course of the crisis. A few strategies to monitor public opinion are presented in Table 8.

Monitoring public opinion will enable you to:

- understand audiences better;
- understand what message framing resonates with target audiences;
- efficiently and adequately respond to rumours and misconceptions;
- continuously update and adjust communication strategy to build resilience against vaccine safety scares;
- reach communication goals.

In addition to information gathering through personal and professional networks and traditional media, subscribe to services that offer social media monitoring with daily reports of key topics and trends. Check the most relevant web pages and social media regularly to keep track of the debate on vaccines and immunization. This will allow you to plan, update and adjust your communication strategy accordingly.

Table 8. Strategies to monitor public opinion

CONDUCT SOCIAL MEDIA MONITORING	There are many services and programmes available to identify, gather and analyse relevant social media conversations and trends in public opinion.
TRADITIONAL MEDIA	Follow reporting and public comments on national and international news services.
CONDUCT RAPID ANALYSIS	Obtain an understanding of knowledge levels and attitudes to vaccination, service provision and health authorities through qualitative or quantitative research (e.g. with focus groups or online surveys respectively).
GATHER INFORMATION FROM A PUBLIC INFORMATION HOTLINE OR CHATBOT	Establish a telephone or chat information hotline for questions from the public. Register and analyse questions. Make sure that you allocate sufficient human and budgetary resources to establish and maintain such a hotline. Trained staff should operate the hotline to ensure that evidence-based information is spread. Further, staff should be trained in responding to people with concerns and fears about immunization.
GATHER INFORMATION FROM FRONTLINE HEALTH WORKERS	Ask health workers to report back to you about questions asked by parents, caregivers, patients and the public; particularly, if new questions are being asked and new misperceptions seem to be taking hold.
USE YOUR NETWORK	Ask your group of stakeholders, colleagues, partner organizations, professional associations, friends, families and relatives about their opinions and perceptions. Ask them to inform you, if they hear of any rumours circulating.

Brief spokespersons

Ideally, spokespersons should be trained in crisis and media management during the preparedness phase. Spokespersons should be well briefed and consider the following when. In preparing for an interview:

- Find out what specific issues related to the crisis are to be discussed.
- Understand the media agenda/angle.
- Clarify what the interviewer and interview hope to achieve.
- Prepare key messages accordingly.
- Double check facts.
- Consider whether they are the right persons to answer the expected questions.
- Clarify who will conduct the interview, how long it will be and whether it is live or pre-recorded.
- Find out who else will be interviewed, and investigate their likely agenda/angle. Consider declining to participate if a 'panel discussion' will display false balance (e.g. give equal air time to evidence and non-evidence based opinions).
- Simulate possible scenarios – and be prepared to manage uncertainty.
- Train, rehearse and prepare in detail.

Communicate with the public

It is essential to choose an appropriate response to a crisis or a vaccine-related event to maintain the public's trust in vaccination. When choosing an appropriate response, you should analyse the situation (type of event, target audience etc.) so as to respond in a balanced manner (see 1.2 Knowing when to communicate).

When communicating with the public, consider the following:

- If time allows, test messages on a small, representative group to identify those that are most understandable and effective.
- Try to be the first to communicate news – whether good or bad. This allows you to affect how the event is presented before someone else shapes the narrative. Be careful and analyse the situation carefully, as you do not wish to create unnecessary concern.
- Regularly update the public on progress made; use various channels to communicate updates (websites, media, social media, hotlines, meetings with the press).
- Understand the public's attitudes and acknowledge their concerns and fears (also respect behaviours related to beliefs, culture and risk perception). Prepare messages to try to bridge the information gap between the experts and the public.
- Be highly visible and proactive if the situation requires it.
- Try to ensure all stakeholders speak with one voice.
- Avoid attacking the credibility of those with high perceived credibility, even if you do not agree with them.
- Seek, engage and make extensive use of support from credible third parties (influencers, academia, technical experts and others).
- When communicating with the public, try to make your actions visible. For example, if a prominent representative from the ministry of health visits the school where an AEFI occurred, to speak to parents and teachers and listen to their concerns, make sure this is communicated in a tangible, visible way, if appropriate.

Communicate with the media

In some situations, you will need to respond to requests from the media; in others, you will want to be proactive and catch or increase the attention of the media. This may be necessary if you wish to shape the narrative and present the target audience with facts before someone else presents a misinformed story about the event.

When engaging with the media, remember to involve and inform everyone in the vaccine crisis coordination group and also share information with the larger stakeholder group. This prevents mixed messaging. Brief them about the situation, share prepared messages and be transparent about the next steps. When engaging with the media, be sure to be well prepared. Make sure spokespersons are trained and have:

- a clear understanding of all relevant facts (both regarding the event and your country's immunization-related context);
- prepared key messages and answers to all possible difficult questions that may be asked;
- a good relationship with the media (know who will follow the conditions agreed upon and who shows fair and balanced views, and also which media outlets are followed and trusted by your key audiences);
- a clear understanding of which channels best work for your target audience (hotlines, social media, radio, television, other);
- a good relationship with key stakeholders, including community leaders.

Continue response

Throughout the vaccine crisis, ensure a high level of responsiveness and adjust activities to the situation.

Public concerns and fears may evolve, and new themes emerge. These need to be identified and may require a response. Once created, rumours can circulate quickly among people who are uncertain, lack evidence-based information or follow a specific agenda.

Use this checklist to continue your response.

Continue to:

- coordinate with and inform all members of the vaccine crisis coordination group
- monitor public opinion, including media monitoring to identify trends and new developments
- engage active and passive influencers
- update spokespersons
- regularly update and interact with the media
- update and meet with stakeholders regularly
- regularly update key messages and question and answer (Q&A) sheets
- inform the public
- listen to the public's concerns and fears and respond effectively.

For further information consult the following documents:

- Tips for spokespersons *(24)*
- The questions journalists always ask in a crisis *(25)*
- Strategies used by journalists *(26)*

EVALUATION – A BRIEF OVERVIEW

In the evaluation phase, the communication response to the vaccine crisis event should be reviewed to identify lessons learned. Explore whether the goal and objectives identified were reached, and what actions could be taken to achieve better results in the future (although it may not always be easy to gauge whether the goal of maintaining trust has been achieved).

Special attention should be paid to:

- coordination within the vaccine crisis coordination group and other key stakeholders
- processes related to transparency and communication with the public
- understanding the perspectives of the public and key audiences
- choice of messages and communication channels and their effectiveness.

Although the vaccine crisis might be over, the preparation phase for a new potential crisis has already started. This means that all relevant stakeholders need to be aware of their roles and to keep monitoring public perceptions regarding vaccination.

At this stage, the key actions outlined in Table 9 should be considered.

Table 9. Post-crisis assessment – key communicaitons actions

KEY ACTION	RECOMMENDATION
CONDUCT A POST-CRISIS REVIEW	Every crisis represents an opportunity to create stronger and more resilient programmes to manage vaccine-related events better in the future. To this end, it is important to conduct a post-crisis review of the communication response to a crisis. For sample evaluation/review questions, see Annex 2.
IDENTIFY LESSONS LEARNED	The post-crisis review serves the purpose of identifying lessons learned as well as strengths and weaknesses in communications activities of the programme. Based on this analysis, changes can be made to improve future responses to potential vaccine crises.
SHARE RESULTS WITH KEY STAKEHOLDERS AND PARTNERS	Prepare a report with lessons learned and share them with the vaccine crisis coordination group and other key stakeholders. In this report, point out what worked well and what could be improved in the future (e.g. was mixed messaging an issue or were all stakeholders and communication channels aligned?). Make sure that this report is conveyed in a written format, so that it can inform future crisis responses or, where available, revise the national crisis communication plan/strategy accordingly (e.g. if mixed messaging was an issue, make sure to include a section on how messages can be better aligned and disseminated among stakeholders to ensure that all official communication channels speak with one voice).

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ANNEX 1. BEST PRACTICE CASE STUDIES OF MEDIUM AND HIGH IMPACT VACCINE CRISES

CASE EXAMPLE I: MEDIUM IMPACT EVENT

In country A it was announced that the largest national television channel would broadcast a special feature about a new anti-vaccination documentary featuring one of the country's main social media bloggers and influencers. Worryingly, the feature would reproduce three myths related to vaccination, including the false information that the measles vaccine causes autism and that natural immunity suffices to protect against infectious diseases. The country's health authorities were immediately alarmed, as they could not predict whether the feature would be further picked up by other media platforms, including other television channels, radio and social media, and to what extent this would impact the public's confidence in vaccines.

To this end, the following measures were undertaken to intensify preparedness efforts:

- The feature was recorded and archived as documentation material for the future.
- All information sheets and Q&A tackling the three myths were updated and promoted to further strengthen public resilience against vaccine safety scares.
- Staff involved in crisis management watched the anti-vaccination documentary.
- Messages were developed to state the authorities' view on the documentary to be used reactively, if needed.
- Social media and traditional media channels were monitored regarding the public's response to the documentary and the national feature.
- A stakeholder network, including the media, was immediately activated, and key messages were shared.

The WHO Regional Office for Europe was immediately notified; additional communication materials were sent.

Ultimately, the feature was not picked up by a wider audience and no further action was needed. Nevertheless, preparedness efforts were used to strengthen routine communication and manage a situation which could have easily developed into a high impact event.

CASE EXAMPLE II: HIGH IMPACT EVENT

Following the successful introduction of the HPV vaccine in country B, the increasing spread of misinformation regarding the safety of the vaccine and the broadcasting of a critical documentary fuelled concerns among the population. Vaccine coverage dramatically decreased over a period of two years, from more than 90% of the annual cohort to less than 50%. In response, a partnership between the country's health authorities, cancer society and medical association was formed.

The following measures were taken to curb the crisis, increase confidence in vaccination and ultimately increase immunization coverage to protect more girls against cervical cancer.

- Two key messages were chosen to guide communication goals: "There is a safe and effective vaccine to prevent cervical cancer" and "Every day one woman gets diagnosed with cervical cancer in country B.
- Prior to choosing a communication channel, focus group interviews and surveys were conducted to find out where parents look for information on vaccination (result: Facebook) and who the main decision-makers with regard to HPV vaccination were (result: mothers). As a result, an information and community engagement strategy was launched to target mothers on Facebook.
- A dedicated Facebook page and website were set up to share evidence-based information and respond to concerns.
- Strict branding guidelines were implemented to highlight aligned messaging and show that all stakeholders were on the same page, communicating with visibility, transparency and professionalism.s
- Personal stories were included of women with cervical cancer.
- The Facebook site was monitored 24/7.

A so-called "pull communication" strategy was used when responding to comments: other members were encouraged to respond first; where necessary, authorities responded to comments to provide further information and strengthen evidence-based knowledge.

This comprehensive, proactive communication strategy helped country B in curbing the crisis and largely re-establishing confidence in the HPV vaccine. Within 3 years, coverage with the HPV vaccine in country B increased from a mere 28% in a specific birth cohort to 81% in that cohort. Coverage also increased in other birth cohorts. In addition, after the campaign, in response to a survey 70% of Facebook users reacted positively towards HPV vaccination, compared to only 46% prior to the campaign. While 15% were opposed prior to the campaign, this number dropped to a mere 7% after the campaign.

ANNEX 2. SAMPLE EVALUATION QUESTIONS

Did you and your vaccine crisis coordination group successfully manage to curb the crisis? Have you maintained or re-established public trust?

Consider the questions in Table A2.1 in your evaluation phase.

Table A2.1. List of sample questions – evaluation phase

OVERALL FEEDBACK AND EVALUATION
• How successfully was this crisis handled? • Was the overall response to the crisis effective? Was it conducted in a timely and rapid manner? • Did you reach your overall communication goal? • What shortcomings were identified? What could have been done better and how, in case of a new vaccine crisis? • Were vulnerable, at-risk and marginalized populations sufficiently taken into account? • Was there a budget allocated to vaccine crisis management, including additional human resources as needed? If yes, were these resources sufficient?

IMMUNIZATION COMMUNICATION WORKING GROUP AND STAKEHOLDER MANAGEMENT
• Was the crisis response group or a different response mechanism established and activated in time? • Were all key stakeholders engaged? • Were all key stakeholders well informed at every stage of the process? • Were all key stakeholders responsive and did they act according to their responsibilities and roles? • Did you notice any conflicts of interest among the stakeholders involved? • How could staff be better prepared for a future crisis (e.g. targeted training sessions)?

RELATIONS WITH THE PUBLIC
• Was the public informed in a timely and transparent manner? • Were the public's concerns and fears taken into account in an adequate manner? • Were the public's concerns and fears monitored throughout all phases of the process? • Was the two-way listening strategy incorporated in every phase of the process? • Did all stakeholders respond well to media requests? • Where you able to effectively respond to public concerns?

The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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WORLD HEALTH ORGANIZATION

REGIONAL OFFICE FOR EUROPE

UN City, Marmorvej 51,
DK-2100 Copenhagen Ø, Denmark

Tel.: +45 45 33 70 00 Fax: +45 45 33 70 01

Email: eurocontact@who.int

Website: www.euro.who.int

Statement

Helsinki District Court, Finland, 12 April 2024

COVID-19 Vaccines Safety and Efficacy

by Dr Aseem Malhotra MD for Mika Vauhkala

Short Biodata:

Dr Aseem Malhotra is an NHS trained Consultant Cardiologist and an internationally renowned expert in the prevention, diagnosis and management of heart disease. His areas of expertise include evidence-based medicine and collaborative shared decision-making with patients.

From 2018 - 2023 he was visiting professor of evidence-based medicine at the Bahiana school of medicine and public health, Salvador, Brazil. He is a founding member of Action on Sugar and was the lead campaigner highlighting the harm caused by excess sugar consumption in the United Kingdom, particularly its role in type 2 diabetes and obesity. In 2015 he helped co-ordinate the Choosing Wisely campaign by the Academy of Medical Royal Colleges as lead author in a BMJ paper to highlight the risks of overuse of medical treatments. In the same year he became the youngest member to be appointed to the board of trustees of UK health think tank, The King's Fund that advises government on health policy. Aseem is a frequent expert commentator in print and broadcast media and he has written scores of articles for a number of publications including the BMJ, British Journal of Sports Medicine, BMJ Open Heart, JAMA Internal Medicine, Prescriber, The Pharmaceutical Journal, European Scientist, The Guardian and Observer, BBC online, Huffington Post, The Daily Mirror, Daily Mail, The Daily Telegraph and the Washington Post. He is serves on the editorial board of the Journal of Metabolic Health.

Aseem has appeared in the Health Service Journal’s list of top 50 BME pioneers, and has won a number of awards for his work to raise awareness of diet-related illness both in the UK and internationally. He is a pioneer of the lifestyle medicine movement in the UK and has had feature articles written about him in the New York Times, The Guardian, The Telegraph, The i, and Healthcare Leader. In 2018 he was ranked by software company Onalytica as the number 1 doctor in the world influencing obesity thinking.

In 2016 he was named in the Sunday Times Debrett's list as one of the most influential people in science and medicine in the UK in a list that included Professor Stephen Hawking. His total Altmetric score (measure of impact and reach) of his medical journal publications since 2013 is over 10,000 making it one of the highest in the World for a clinical doctor during this period. His first book co-authored with Donal O' Neill, The Pioppi Diet, has become an international best seller. His second book, the 21 day immunity plan is a Sunday Times best seller. During the first year of the Covid pandemic he was asked by the Secretary of State for Health, Matt Hancock to advice on the link between covid and obesity and how best to reduce population risk to infection. His recently published third book A Statin Free Life is already a best seller.

Award winning American Science Journalist Gary Taubes describes Aseem as someone who has “probably done more in the UK to inject sanity in to nutrition science and the pharmaceutical industry debate than any human being alive”.

Sir Richard Thompson, Past President of the Royal College of Physicians and former personal physician to her majesty The Queen said “Dr Aseem Malhotra is changing the face of medicine and his revolutionary book the Pioppi Diet should be read by everyone”.

The Mayor of Manchester Andy Burnham said “ He’s really making people think differently about what they eat and how they live their life. Through his work he’s going to change many thousands of lives, millions of lives for the better”.

https://draseemmalhotra.co.uk/

Summary

In response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), several new pharmaceutical agents have been administered to billions of people worldwide, including the young and healthy at little risk from the virus. Considerable leeway has been afforded in terms of the pre-clinical and clinical testing of these agents, despite an entirely novel mechanism of action and concerning biodistribution characteristics.

Re-analysis of randomised controlled trials using the messenger ribonucleic acid (mRNA) technology suggests a greater risk of serious adverse events from the vaccines than being hospitalised from COVID-19. Pharmacovigilance systems and real-world safety data, coupled with plausible mechanisms of harm, are deeply concerning, especially in relation to cardiovascular safety. Mirroring a potential signal from the Pfizer Phase 3 trial, a significant rise in cardiac arrest calls to ambulances in England was seen in 2021, with similar data emerging from Israel in the 16–39-year-old age group.

In parallel, authorities and sections of the medical profession have supported unethical, coercive, and misinformed policies such as vaccine mandates and vaccine passports, undermining the principles of ethical evidence-based medical practice and informed consent. These regrettable actions are a symptom of the 'medical information mess': The tip of a mortality iceberg where prescribed medications are estimated to be the third most common cause of death globally after heart disease and cancer. Underlying causes for this failure include regulatory capture – guardians that are supposed to protect the public are in fact funded by the corporations that stand to gain from the sale of those medications.

To gain a better understanding of the true benefits and potential harms of the messenger ribonucleic acid (mRNA) coronavirus disease (COVID) vaccines, I conducted a narrative review of the evidence from randomised trials and real world data of the COVID mRNA products with special emphasis on BioNTech/Pfizer vaccine[1].

In a second published review, I identified the major root causes of these public health failures, it was found that the public health messaging has also resulted in wanton waste of resources and a missed opportunity to help individuals lead healthier lives with relatively simple – and low cost – lifestyle changes[2].

Key aspects of these reviews for 2020-2021 will be developed here for the case of Mr Vauhkala.

I - Safety and Efficacy of the COVID-19 Vaccines up to end 2021

A doctor's experience

Volunteering in a vaccine centre, I was one of the first to receive two doses of Pfizer's messenger ribonucleic acid (mRNA) vaccine, at the end of January 2021. Although I knew my individual risk was small from COVID-19 at age 43 with optimal metabolic health, the main reason I took the jab was to prevent transmission of the virus to my vulnerable patients. During early 2021, I was both surprised and concerned by a number of my vaccine-hesitant patients and people in my social network who were asking me to comment on what I regarded at the time as merely 'anti-vax' propaganda.

But a very unexpected and extremely harrowing personal tragedy was to happen a few months later that would be the start of my own journey into what would ultimately prove to be a revelatory and eye-opening experience so profound that after six months of critically appraising the data myself, speaking to eminent scientists involved in COVID-19 research, vaccine safety and development, and two investigative medical journalists, I have slowly and reluctantly concluded that contrary to my own initial dogmatic beliefs, Pfizer's mRNA vaccine is far from being as safe and effective as we first thought.

This critical appraisal is based upon the analytical framework for practicing and teaching evidence-based medicine, specifically utilising individual clinical expertise and/or experience

[1] Malhotra, A. (2022a). Curing the pandemic of misinformation on COVID-19 mRNA vaccines through real evidence-based medicine - Part 1. Journal of Metabolic Health, 5(1), 8 pages. doi:https://doi.org/10.4102/jir.v5i1.71

[2] Malhotra, A. (2022b). Curing the pandemic of misinformation on COVID-19 mRNA vaccines through real evidence-based medicine - Part 2. Journal of Metabolic Health, 5(1), 10 pages. doi: https://doi.org/10.4102/jir.v5i1.72

with use of the best available evidence and taking into consideration patient preferences and values.

A case study

Case studies are a useful way of conveying complex clinical information and can elicit useful data that would be lost or not be made apparent in the summary results of a clinical trial.

On 26 July 2021, my father, Dr Kailash Chand OBE, former deputy chair of the British Medical Association (BMA) and its honorary vice president (who had also taken both doses of the Pfizer mRNA vaccine six months earlier) suffered a cardiac arrest at home after experiencing chest pain. A subsequent inquiry revealed that a significant ambulance delay likely contributed to his death[3]. But his post-mortem findings are what I found particularly shocking and inexplicable. Two of his three major arteries had severe blockages: 90% blockage in his left anterior descending artery and a 75% blockage in his right coronary. Given that he was an extremely fit and active 73-year-old man, having walked an average of 10–15 000 steps/day during the whole of lockdown, this was a shock to everyone who knew him, but most of all to me. I knew his medical history and lifestyle habits in great detail. My father who had been a keen sportsman all his life, was fitter than the overwhelming majority of men his age. Since the previous heart scans (a few years earlier, which had revealed no significant problems with perfect blood flow throughout his arteries and only mild furring), he had quit sugar, lost belly fat, reduced the dose of his blood pressure pills, started regular meditation, reversed his prediabetes and even massively dropped his blood triglycerides, significantly improving his cholesterol profile.

I couldn't explain his post-mortem findings, especially as there was no evidence of an actual heart attack but with severe blockages. This was precisely my own special area of research. That is, how to delay progression of heart disease and even potentially reverse it. In fact, in my own clinic, I successfully prescribe a lifestyle protocol to my patients on the best available evidence on how to achieve this. I've even co-authored a high-impact peer-reviewed paper with two internationally reputed cardiologists (both editors of medical journals) on shifting the paradigm on how to most effectively prevent heart disease through lifestyle changes[4].We emphasised the fact that coronary artery disease is a chronic inflammatory condition that is exacerbated by insulin resistance.

In November 2021, I was made aware of a peer-reviewed abstract published in *Circulation*, with concerning findings. In over 500 middle-aged patients under regular follow up, using a predictive score model based on inflammatory markers that are strongly correlated with risk of heart attack, **the mRNA vaccine was associated with significantly increasing the predictive risk[5] of a coronary event within five years from 11% pre-mRNA vaccine to 25% 2–10 weeks post mRNA vaccine**. An early and relevant criticism of the validity of the findings was that there was no control group, but nevertheless, even if partially correct, that would mean that there would be a large acceleration in progression of coronary artery disease, and more importantly heart attack risk, within months of taking the jab[6]. I wondered whether my father's Pfizer vaccination, which he received six months earlier, could have contributed to his unexplained premature death and so I began to critically appraise the data.

Questioning the Data

I recalled a cardiologist colleague of mine informing me, to my astonishment at the time, that he had made a decision not to take the vaccine for a number of reasons, including his

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[3] Gallagher P. The death of Dr Kailash Chand: How a lethal mix of NHS privatisation and lack of resources led to tragedy [Homepage]. iNews. 2021 [accessed 2023 Nov 17]. https://inews.co.uk/news/health/the-death-of-dr-kailash-chand-how-a-lethal-mix-of-nhs-privatisation-and-lack-of-resources-led-to-tragedy-1303449

[4] Malhotra A, Redberg RF, Meier P. Saturated fat does not clog the arteries: Coronary heart disease is a chronic inflammatory condition, the risk of which can be effectively reduced from healthy lifestyle interventions. Br J Sports Med. 2017;51(15):1111–1112. https://doi.org/10.1136/bjsports-2016-097285

[5] *Predictive risk*: this study used the PULS Cardiac Test (Predictive Health Diagnostics Co., Irvine, CA) a clinically utilized measurement of multiple protein biomarkers, which generates a score predicting the 5 year risk (percentage chance) of a new Acute Coronary Syndrome (ACS) called the PULS Score. This clinic has been using the PULS Cardiac Test (Predictive Health Diagnostics Co., Irvine, CA) a clinically utilized measurement of multiple protein biomarkers, which generates a score predicting the 5 yr risk (percentage chance) of a new Acute Coronary Syndrome (ACS) called the PULS Score.

[6] Gundry SR. Abstract 10712: Observational findings of PULS cardiac test findings for inflammatory markers in patients receiving mRNA vaccines. Circulation. 2021;144(Suppl_1):A10712. https://doi.org/10.1161/circ.144.suppl_1.10712

personal low background COVID-19 risk[7,8] and concerns regarding unknown short- and longer-term harms. One thing that alarmed him about Pfizer's pivotal mRNA trial published in *The New England Journal of Medicine,* in December 2020, was the data in the supplementary appendix, specifically that there were four cardiac arrests in those who took the vaccine versus only one in the placebo group[9].These figures were small in absolute terms and did not reach statistical significance in the trial, suggesting that it may just be coincidence, but without further studies it was not possible to rule out this being a genuinely causal relationship (especially without access to the raw data), in which case it could have the effect of causing a surge in cardiac arrests once the vaccine was rolled out to tens of millions of people across the globe. In terms of efficacy, headlines around the world made very bold claims of 95% effectiveness, the interchangeable use of 'efficacy' and 'effectiveness' glossing over the big difference between controlled trial and real-world conditions[10].

Contrary to popular belief**, what the Pfizer pivotal efficacy trial did not show was any statistically significant reduction in serious illness or COVID-19 mortality from the vaccine over the 6-month period of the trial**, **but the actual numbers of deaths (attributed to COVID-19) are still important to note**. There were only two deaths from COVID-19 in the placebo group and one death from COVID-19 in the vaccine group. Looking at all-cause mortality over a longer period, there were actually slightly more deaths[11] in the vaccine group (19 deaths) than in the placebo group (17 deaths). Also of note was the extremely low rate of COVID-19 illness classified as severe in the placebo group (nine severe cases out of 21 686 subjects, 0.04%), reflecting a very low risk of severe illness even in regions chosen for the trial because of perceived high prevalence of infection.

Now that we know what the published trial did and did not show in terms of the vaccine efficacy, we can attempt to extrapolate what the effect of the vaccine would be in reducing mortality or any other adverse outcome from the virus.

Clinical Harms

Concerns have already been raised about the under-reporting of adverse events in the clinical trials for the COVID-19 vaccines. Investigative medical reporter Maryanne Demasi analysed the various ways that the pivotal mRNA trials failed to account for serious harms[12]. Not only were trial participants limited to the type of adverse event they could report on their digital apps, but some participants who were hospitalised after inoculation were withdrawn from the trial and not reported in the final results. After two months into the pivotal trials, the FDA allowed vaccine companies to offer the vaccine to subjects in the placebo group, essentially torpedoing any chance of properly recording adverse events from that point on, forcing a reliance of pharmacovigilance data.

Such data have shown that one of the most common mRNA COVID-19 vaccine-induced harms is myocarditis. A study across several Nordic countries showed an increased risk from mRNA vaccination over background, especially in young males[13]. Authorities have repeatedly maintained that myocarditis is more common after COVID-19 infection than after vaccination[14]. However, trial data demonstrating that vaccination reduces the risk of myocarditis in subsequent infection is elusive, and in fact the risks may be additive. Incidence

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[7] Axfors C, Ioannidis JPA. Infection fatality rate of COVID-19 in community-dwelling elderly populations. Eur J Epidemiol. In press 2022;37(3):235–249. https://doi.org/10.1007/s10654-022-00853-w

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[11] Wollersheim S, Schwartz A. BLA Clinical Review Memorandum* [Homepage]. 2021 [accessed 2023 Nov 17]. https://www.fda.gov/media/152256/download

[12] Demasi M. Are adverse events in Covid-19 vaccine trials under-reported? [homepage]. Investigative Journalism. Nov 2021 [accessed 2023 Nov 17]. Available from https://maryannedemasi.com/publications/f/are-adverse-events-in-covid-19-vaccine-trials-under-reported

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[14] Patone M, Mei XW, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 2022;28:410422. .https://doi.org/10.1038/s41591-021-01630-0
Note:the same authors had already warned about this risk earlier in 2021 https://www.phc.ox.ac.uk/publications/1225727

of myocarditis rocketed from spring 2021 when vaccines were rolled out to the younger cohorts having remained within normal levels for the full year prior, despite COVID-19[15], with the most up-to-date evidence, a paper from Israel[16] presented the results of a large population-based retrospective cohort study of 196,992 adults after COVID-19 infection in Clalit Health Services members in Israel between March 2020 and January 2021. The study found that the infection itself, prior to roll-out of the vaccine, conferred no increase in the risks of either myocarditis or pericarditis from COVID-19, strongly suggesting that the increases observed in earlier studies were because of the mRNA vaccines, with or without COVID-19 infections as an additional risk in the vaccinated[16].

Indeed, this reflects my own clinical experience of advising and managing several patients in the community who presented with a clear suggestion from the history of myocarditis post mRNA vaccination but aren't necessarily unwell enough to require hospital admission. Many case studies can be presented to demonstrate this.

II – Evidence-based Medical & Public Health Decision-Making in question

Health System Indicators

A number of reports and retrospective studies on 2020-2021 have produced concerning rates of myocarditis, depending on age, ranging from 1 in 6000 in Israel[17] to 1 in 2700 in a Hong Kong study in male children and adolescents aged 12–17 years[18]. Most of the epidemiology studies that have been carried out have measured myocarditis cases that have been diagnosed in a hospital setting, and do not claim to be a comprehensive measure of more mild cases (from which long-term harm cannot be ruled out). In addition, under-reporting of adverse events is the scourge of pharmacovigilance data[19].

It is instructive to note that according to ambulance service data**, in 2021 (the year of the vaccine roll-out), there were approximately an extra 20 000 (~20% increase) out-of-hospital cardiac arrest calls compared to 2019, and approximately 14 000 more than in 2020**. Data obtained under Freedom of Information laws from one of the largest ambulance trusts in England suggest that **there was no increase from November 2020 to March 2021, and thereafter the rise has been seen disproportionately in the young**[20]. This is a huge signal that surely needs investigating with some urgency[21].

Similarly, a scientific report published in *Nature*, comparing cardiovascular emergency events during January–May 2021 with the years 2019–2020[22] on the basis of Israel Government Data base Portal vaccination data revealed a **25% increase in both acute coronary syndrome and cardiac arrest calls in the 16- to 39-year-old age groups significantly associated with administration with the first and second doses of the mRNA vaccines but no association with COVID-19 infection**[23].

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[15] Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and pericarditis after vaccination for COVID-19. JAMA. 2021;326(12):1210–1212. https://doi.org/10.1001/jama.2021.13443

[16] Tuvali O, Tshori S, Derazne E, et al. The incidence of myocarditis and pericarditis in post COVID-19 unvaccinated patients-a large population-based study. J Clin Med Res. 2022;11(8):2219. https://doi.org/10.3390/jcm11082219

[17] Fronza M, Thavendiranathan P, Chan V, et al. Myocardial injury pattern at MRI in COVID-19 vaccine-associated myocarditis. Radiology. 2022;304(3):553–562. https://doi.org/10.1148/radiol.212559
Note: included In this retrospective cohort study, consecutive adult patients with myocarditis with at least one T1-based and at least one T2-based abnormality at cardiac MRI performed at a tertiary referral hospital from December 2019 to November 2021.

[18] Chua GT, Kwan MYW, Chui CSL, et al. Epidemiology of acute myocarditis/pericarditis in Hong Kong adolescents following comirnaty vaccination. Clin Infect Dis. 2021; ciab989. https://doi.org/10.1093/cid/ciab989

[19] Gahr M, Eller J, Connemann BJ, Schönfeldt-Lecuona C. Underreporting of adverse drug reactions: Results from a survey among physicians. Eur Psychiatry. 2017;41:S369. https://doi.org/10.1016/j.eurpsy.2017.02.377

[20] Patients with heart conditions/strokes from 2017-present day [homepage]. WhatDoTheyKnow; 2022 [accessed 2023 Nov 17]. https://www.whatdotheyknow.com/request/patients_with_heart_conditionsst

[21] HART. An epidemic of cardiac arrests [Homepage]. HART. HART Group; 2022 [accessed 2023 Nov 17]. https://www.hartgroup.org/an-epidemic-of-cardiac-arrests/

[22] Data on the vaccinations and COVID-19 cases were obtained from the online Israel Government Database Portal (https://info.data.gov.il/datagov/home/). These data include the number of daily administered 1st and 2nd vaccination doses by age group, as well as the weekly number of new confirmed COVID-19 cases by age group, across all of Israel

[23] Sun CLF, Jaffe E, Levi R. Increased emergency cardiovascular events among under-40 population in Israel during vaccine rollout and third COVID-19 wave. Scientific Reports, Nature 2022;12(1):6978. https://doi.org/10.1038/s41598-022-10928-z

The authors state that:

"The findings raise concerns regarding vaccine-induced undetected severe cardiovascular side effects and underscore the already established causal relationship between vaccines and myocarditis, a frequent cause of unexpected cardiac arrest in young individuals".

Reporting Systems Data

The United Kingdom relies on the Medicines and Health Regulatory Agency's (MHRAs) 'Yellow Card' reporting system[24], which is far from adequate to cope with a rapid roll-out of a brand-new product. It only detected the clotting problems that resulted in the withdrawal of the AstraZeneca product in April 2021 for younger people after 9.7 million doses had been given in the United Kingdom[25]; in contrast, Denmark detected the problem after only 150 000 doses had been administered[26].

In the United Kingdom, since the vaccine roll-out there have been almost 500 000 adverse event reports recorded (via the Yellow Card system) in association with the mRNA COVID-19 vaccinations involving over 150 000 individuals. In terms of the number of reports per person (i.e. having received at least one dose), the MHRA figures show around 1 in 120 suffering a likely adverse event that is beyond mild[27]. However, the MHRA are unclear about the rate and furthermore do not separate out the serious adverse events. Nevertheless, this level of reporting is unprecedented in the modern medical era and equals the total number of reports received in the first 40 years of the Yellow Card reporting system (for all medicines – not just vaccines) up to 2020[28]. In comparison, for the measles, mumps and rubella (MMR) vaccine, the number of reports per person vaccinated was around 1 in 4000, more than thirty times less frequent than the 1 in 120 Yellow Card reports for COVID-19 vaccine recipients[28].

Norway does separate out the reported serious adverse reactions and has shown a rate of approximately 1 in 1000 after two doses of BioNTech/Pfizer mRNA product that result in hospitalisation or are life changing[29].

Another, and more useful, source of information (because of the level of detail for each report made available to the public) is **the United States (US) Vaccine Adverse Effect Reporting System (VAERS)**. As with the UK's system, the level of reports – including serious ones – associated with COVID-19 vaccines is completely unprecedented. For example, over 24 000 deaths had been recorded in VAERS as of 02 March 2022; 29% of these occurred within 48 h of injection, and half within two weeks. Earlier as of 15 October 2021, 17'128 deaths had already been recorded, of which 818'044 injuries cases and 26'199 permanent disabilities. An analysis published on 8 September 2021 by Hoeg et al. from this database shows that young people aged 12 to 17 are exposed to a higher cardiac risk (myocarditis type) than the risk of hospitalisation for COVID-19. The group with the most severe risk of heart problems after experimental vaccination is the youngest group of 12-15 year olds

The average reporting rate prior to 2020 was less than 300 deaths per annum. One explanation often given for this is that the COVID-19 vaccine roll-out is unprecedented in

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[24] Coronavirus vaccine – Weekly summary of Yellow Card reporting [Homepage]. GOV.UK. [accessed 2023 Nov 17]. https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

[25] Yellow Card reports compared for Oxford/AstraZeneca and PfizerBioNTech product (2021). Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots. *BMJ:*372:N699 - doi: https://doi.org/10.1136/bmj.n699 (Published 11 March 2021)

[26] BBC News. AstraZeneca vaccine: Denmark stops rollout completely. BBC [serial online]. 2021 [accessed 2023 Nov 17]; https://www.bbc.co.uk/news/world-europe-56744474

[27] Coronavirus vaccine – Weekly summary of Yellow Card reporting [Homepage]. GOV.UK. [accessed 2023 Nov 17]. https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

[28] Medicines and Healthcare products Regulatory Agency. All spontaneous suspected UK Adverse Drug Reaction (ADR) reports associated with the MMR vaccine in 2020 [homepage]. 2021 [accessed 2023 Nov 17] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1041736/FOI_21-877-4.pdf

[29] Norwegian Medicines Agency. Reported suspected adverse reactions to COVID19 vaccines as of 04.01.2022 [Homepage]. 2022 [accessed 2023 Nov 17]. https://legemiddelverket.no/Documents/English/Covid-19/20220107%20Reported%20suspected%20adverse%20reactions%20coronavirus%20vaccines%20-%20updated%2020220113.pdf

Hoeg T.B., Krug A., Stevenson J. and Mandrola J. (2021). SARS-CoV-2 mRNA Vaccination-Associated Myocarditis in Children Ages 12-17: A Stratified National Database Analysis, medRxiv 2021.08.30.21262866; doi: https://doi.org/10.1101/2021.08.30.21262866.

scope; however, this is not valid, since (for the last decade at any rate) the United States has administered 150 million – 200 million vaccinations annually. Another criticism of VAERS is that 'anyone can make an entry', yet, in fact, an analysis of a sample of 250 early deaths suggested that the vast majority are hospital or physician entries[30], and knowingly filing a false VAERS report is a violation of Federal law punishable by fine and imprisonment[31]. Given that **VAERS was set up to generate early signals of potential harm for new vaccines, and was instrumental in doing so for several products, it seems perverse to only now criticise it as unreliable when there seem to have been no changes in the way it operates**.

It has been estimated that serious adverse effects that are officially reported are actually a gross underestimate, and this should be borne in mind when the above comments in relation to VAERS reports are considered. For example, a paper by David Kessler (a former FDA Commissioner) cites data suggesting that as few as 1% of serious adverse events are reported to the FDA[32]. Similarly in relation to the Yellow Card scheme in the United Kingdom, it has been estimated that only 10% of serious adverse effects are reported[33,34]. A pre-print publication co-authored by some of the most trusted medical scientists in the world in relation to data transparency adds validity to pharmacovigilance data. Accessing data from the FDA and Health Canada websites and combining results from journal articles that published the Pfizer and Moderna trials, the authors concluded that the absolute risk of a serious adverse event from the mRNA vaccines (a rate of one in 800) significantly exceeded the risk of COVID-19 hospitalisation in randomised controlled trials[35,36].

What VAERS and other reporting systems will miss are potential medium to longer term harms that neither patients nor doctors will automatically attribute to the drug. For example, if the mRNA vaccine increases the risk of a coronary event within a few months (in what was a likely contributory factor in my father's sudden cardiac death), then this would increase event rates well beyond the first few weeks of the jab yet linking it back to the vaccine, and thus reporting it is highly unlikely to occur later on.

Biological mechanism of harm

For 'conventional vaccines', an inert part of the bacteria or virus is used to 'educate' the immune system. The immune stimulus is limited, localised and short-lived. For the COVID-19 vaccines, spike protein has been shown to be produced continuously (and in unpredictable amounts) for at least four months after vaccination[37] and is distributed throughout the body after intramuscular injection[38]. For the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines, the spike protein was chosen, possibly because it enables cell entry. However, this protein is not inert, but rather it is the source of much of the pathology associated with severe COVID-19, including endothelial damage[39], clotting abnormalities[40] and lung damage. It is instructive to note that prior to roll-out of the mRNA products, the WHO endorsed a priority list of potential serious adverse

[30] McLachlan S, Dube K, Osman M, Chiketero PP. (June 2021). Analysis of COVID-19 vaccine death reports from the Vaccine Adverse Events Reporting System (VAERS) Database: Interim Results and analysis. ResearchGate. https://doi.org/10.13140/RG.2.2.26987.26402

[31] VAERS. Report an adverse event [homepage]. [accessed 2023 Nov 17]. https://vaers.hhs.gov/reportevent.html

[32] Kessler DA. Introducing MEDWatch. A new approach to reporting medication and device adverse effects and product problems. JAMA. 1993;269(21):2765–2768. https://doi.org/10.1001/jama.1993.03500210065033

[33] Rawlins MD. Pharmacovigilance: Paradise lost, regained or postponed? The William Withering Lecture 1994. J R Coll Physicians Lond. 1995;29(1):41–49.

[34] Yellow Card: Please help to reverse the decline in reporting of suspected adverse drug reactions [homepage]. GOV.UK; 2019 [accessed 2023 Nov 17]. https://www.gov.uk/drug-safety-update/yellow-card-please-help-to-reverse-the-decline-in-reporting-of-suspected-adverse-drug-reactions

[35] Fraiman J, Erviti J, Jones M, et al. Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults. Vaccine. 2022 Aug 30:S0264-410X(22)01028-3.

[36] Note for clarity: "the results of both studies reported all data at the time of data cutoff (14 Nov 2020 for Pfizer, 25 Nov 2020 for Moderna)" cited from above reference by Fraiman et al.

[37] Bansal S, Perincheri S, Fleming T, et al. Cutting edge: Circulating exosomes with covid spike protein are induced by BNT162b2 (Pfizer-BioNTech) vaccination prior to development of antibodies: A novel mechanism for immune activation by mRNA vaccines. J Immunol. 2021;207(10):2405–2410. https://doi.org/10.4049/jimmunol.2100637

[38] Seneff S, Nigh G, Kyriakopoulos AM, McCullough PA. Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and MicroRNAs. Food Chem Toxicol. 2022;164:113008. https://doi.org/10.1016/j.fct.2022.113008

[39] Lei Y, Zhang J, Schiavon CR, et al. SARS-CoV-2 spike protein impairs endothelial function via downregulation of ACE 2. Circ Res. 2021;128(9):1323–1326. https://doi.org/10.1161/CIRCRESAHA.121.318902

events of special interest that may occur as a direct result of COVID-19 vaccines. The list was based upon the specific vaccine platform, adverse events associated with prior vaccines in general, theoretical associations based upon animal models and COVID-19-specific immunopathogenesis[41].

Evidence-based medicine and COVID-19 vaccine roll-out

Neither the drug regulators nor the vaccine manufacturers have yet to share all the raw data from the pivotal trials for the COVID-19 vaccines[42]. The raw data from clinical trials comprise thousands of pages that have yet to be released for independent scrutiny. This is important because historically when independent researchers have on occasion gained access to this data then it can completely overturn the conclusions of the published trials: A case in point is Tamiflu[43]. Getting access to clinical case reports for Tamiflu ultimately revealed that the drug was no more effective than paracetamol for influenza and also came with small but significant harms. The UK government had spent half a billion dollars stockpiling a drug that in effect proved to be useless despite claims by the manufacturers (Roche, Basel, Switzerland) that it shortened the duration and severity of the illness. The independent researchers who were able to analyse the data concluded that all industry-sponsored research should be considered marketing until proven otherwise.

It is against this backdrop that transparency advocates sued the Food and Drug Administration (FDA) to gain access to the data upon which the Pfizer (BNT162b2) vaccine was granted emergency use authorisation[44]. The FDA wanted a US Federal court judge to allow the agency 55 years to release this data[45]. Why would the FDA – 'which is responsible for the oversight of more than $2.7 trillion in consumption of food, medical products, and tobacco[46]' – do this? Secrecy should never surround any public health intervention. The lawyer acting on behalf of the plaintiff Aaron Siri reported that:

The government also sought to delay full release of the data it relied upon to license this product until almost every American alive today is dead. That form of governance is destructive to liberty and antithetical to the openness required in a democratic society[47].

Instead, the judge ordered the FDA to release the data over a period of eight months after all commercially sensitive information has been redacted.

A major risk factor for failure to protect the public from such harms is lack of independence of the regulator. The FDA's Centre for Drug Evaluation Research (CDER) receives 65% of its funding from the pharmaceutical industry (mainly in the form of user fees)[48]. For example, as part of the approval process for its COVID-19 vaccine, Pfizer made a wire transfer to the FDA

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[40] Ryu JK, Sozmen EG, Dixit K, et al. SARS-CoV-2 spike protein induces abnormal inflammatory blood clots neutralized by fibrin immunotherapy. bioRxiv 10.12.464152 (2021). https://doi.org/10.1101/2021.10.12.464152

[41] Yellow Card: Please help to reverse the decline in reporting of suspected adverse drug reactions [Homepage]. GOV.UK; 2019 [accessed 2023 Nov 17]. https://www.gov.uk/drug-safety-update/yellow-card-please-help-to-reverse-the-decline-in-reporting-of-suspected-adverse-drug-reactions

[42] Doshi P, Godlee F, Abbasi K. Covid-19 vaccines and treatments: We must have raw data, now. BMJ. January 2022;376:o102. https://doi.org/10.1136/bmj.o102

[43] BMJ. Tamiflu campaign [homepage]. [accessed 2023 Nov 17]. https://www.bmj.com/tamiflu

[44] Demasi M. FDA to release Pfizer data but the devil could be in the detail [Homepage]. Investigative Journalism. 2022 [accessed 2023 Nov 17]. https://maryannedemasi.com/publications/f/fda-to-release-pfizer-data-but-the-devil-could-be-in-the-detail?blogcategory=COVID-19

[45] Public Health and Medical Professionals for Transparency vs Food and Drug Administration. Civil Action No. 4:21-cv-01058-P public health and medical professionals for transparency [homepage]. 2021 [accessed 2023 Nov 17]. https://www.sirillp.com/wp-content/uploads/2021/11/020-Second-Joint-Status-Report-8989f1fed17e2d919391d8df1978006e.pdf

[46] US Food and Drug Administration (FDA) Fact sheet: FDA at a glance [Homepage]. Silver Spring, MD: FDA; 2019 [accessed 2023 Nov 17]. https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance

[47] Demasi M. FDA to release Pfizer data but the devil could be in the detail [Homepage]. Investigative Journalism.8 January 2022 [accessed 2023 Nov 17]. https://maryannedemasi.com/publications/f/fda-to-release-pfizer-data-but-the-devil-could-be-in-the-detail?blogcategory=COVID-19

[48] Gagnon MA, Lexchin J. The cost of pushing pills: A new estimate of pharmaceutical promotion expenditures in the United States. PLoS Med. 2008;5(1):e1. https://doi.org/10.1371/journal.pmed.0050001

of $2 875 842 million in May 2021[49] under the *Prescription Drug User Fee Act* of 1992[50]. Full FDA approval for Pfizer's COVID-19 injection duly followed in August 2021[51] despite evidence emerging a few months later that the original RCT data suggested a greater risk of serious adverse events from the vaccine than from hospitalisation because of COVID-19.

Shortcomings of informed decision making in the medical profession

According to Professor Carl Heneghan and urgent care General Practitioner, the director of the University of Oxford's Centre of Evidence-Based Medicine: '*with every intervention you do as a doctor you must ask yourself two questions: how much difference does it make? How do I know this?*[52]'

Building on the Academy of Medical Royal Colleges Choosing Wisely campaign[53], it is instructive to note that the General Medical Council in 2020 issued guidance on the duty of doctors to engage in Shared Decision Making with patients, underpinned by informed consent[54].

There are six components essential to informed decision making:

(1) description of the nature of the decision;
(2) discussion of alternatives;
(3) discussion of risks and benefits (in absolute terms);
(4) discussion of related uncertainties;
(5) assessment of the patient's understanding; and
(6) elicitation of the patient's preference.

If the administration of the vaccine did not adhere to these principles (which is likely widespread, consistent with historical evidence[55]), then it is also a significant breach of General Medical Council duties of a doctor to 'give patients the information they want or need in a way that they can understand'[56].

[49] Pfizer. BLA 125742 COVID-19 mRNA vaccine (BNT162/PF-07302048) part 1 of the original submission – Rolling Biologics License Application (BLA) request for priority review designation [Homepage]. 2021 [accessed 2023 Nov 17]. https://phmpt.org/wp-content/uploads/2022/03/125742_S1_M1_cover.pdf

[50] CONGRESS.GOV. Prescription Drug User Fee Act of 1992 [homepage]. 5952 Sep 24, 1992 [accessed 2023 Nov 17]. http://www.congress.gov/

[51] US Food and Drug Administration (FDA). FDA approves first COVID-19 vaccine [Homepage]. U.S. Food and Drug Administration. FDA; 2021 [accessed 2023 Nov 17]. https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine

[52] Heneghan C, Mahtani KR, Goldacre B, Godlee F, Macdonald H, Jarvies D. Evidence based medicine manifesto for better healthcare. BMJ. 2017;357:j2973. https://doi.org/10.1136/bmj.j2973

[53] Malhotra A, Maughan D, Ansell J, et al. Choosing Wisely in the UK: The Academy of Medical Royal Colleges' initiative to reduce the harms of too much medicine. BMJ. 2015;350:h2308. https://doi.org/10.1136/bmj.h2308

[54] General Medical Council. Shared decision making is key to good patient care – GMC guidance [Homepage]. [accessed 2023 Nov 17]. https://www.gmc-uk.org/news/news-archive/shared-decision-making-is-key-to-good-patient-care---gmc-guidance

[55] Braddock CH 3rd, Edwards KA, Hasenberg NM, Laidley TL, Levinson W. Informed decision making in outpatient practice: Time to get back to basics. JAMA. 1999;282(24):2313–2320. https://doi.org/10.1001/jama.282.24.2313

[56] Duties of a doctor registered with the General Medical Council [Homepage]. Royal College of Surgeons. [accessed 2023 Nov 17]. https://www.rcseng.ac.uk/standards-and-research/gsp/duties-of-a-doctor-registered-with-the-general-medical-council/

In conclusion

There was never any evidence justifying any COVID-19 vaccine mandates, passports or any of the other coercive measures adopted by various governments worldwide. Every patient who was offered any COVID-19 vaccine should have been made aware of what their risk from COVID-19 is according to age and risk factors. In keeping with ethical medical practice, doctors should have informed patients of their absolute risk reduction for infection from previous more lethal variant being approximately 0.84% or 1 in 119 (based on non-transparent data) and that this level of protection only lasts for a few months. They should also have provided more precise and robust data on what the actual absolute individual risk reduction of COVID-19 death from the vaccine is, what the true rates of serious adverse events (such as permanent disability, hospitalisation or death) are. It is only when doctors and patients have all this information that they can then be empowered to have frank decision making conversations on whether any treatment – including this vaccine – is right for them. The profession must explain that optimising metabolic health will give patients the best chance for ensuring they are not just resilient to infection but reducing their risk of chronic disease including heart disease, cancer and dementia.

The time has come to stop misleading evidence flowing downstream into media reporting and clinical decision making and resulting in unethical and unscientific policy decisions. It's time for real evidence-based medicine[57]

The most objective determinant of whether the benefits of the vaccines outweigh the harms is by analysing its effects on 'all-cause mortality'. This gets round the thorny issue as to what should be classified as a COVID-19 death, and also takes full account of any negative effects of the vaccine. It would be surprising – to say the least – if during an apparently deadly pandemic, an effective vaccine could not clearly and unequivocally be shown to reduce all-cause mortality.

Pfizer's pivotal mRNA trial in adults did not show any statistically significant reduction in all-cause mortality, and in absolute terms there were actually more deaths in the treatment arm versus in the placebo.

There is also a strong scientific, ethical and moral case to be made that the current mRNA vaccine administration must stop until Pfizer releases all the raw data for independent scrutiny[58].This will allow a more accurate understanding of which groups are more likely to potentially benefit from the vaccine versus those who are more likely to be harmed. A pause and reappraisal of vaccination Policies for COVID-19 is long overdue[59].

The above reviews of data and studies conducted in 2020-2021 present the evidence that the risks of adverse events from the vaccine remain constant, whereas the benefits reduce over time, as new variants are (1) less virulent and (2) not targeted by an outdated product.

From my medical experience and the review of sound data and scientific basis, I can confirm that in December 2021 the medical and scientific communities should have known that COVID-19 vaccines were proven to be far from safe or effective and far from preventing transmission of COVID-19 or severe form of COVID-19. Most of them did not know. Although the results were available and showed early on in 2021 a higher risk of deleterious reactions such as cardiovascular events. The COVID-19 vaccine study should have ethically been halted and reconsidered.

Looking to the future the medical and public health professions must recognise these failings and eschew the tainted dollar of the medical-industrial complex. It will take a lot of time and effort to rebuild trust in these institutions, but the health – of both humanity and the medical profession – depends on it[60].

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[57] Greenhalgh T, Howick J, Maskrey N, Evidence Based Medicine Renaissance Group. Evidence based medicine: A movement in crisis? BMJ. 2014;348:g3725. https://www.bmj.com/content/348/bmj.g3725

[58] BMJ. Tamiflu campaign [Homepage].[cited in Malhotra 2022, accessed 2023 Nov 17]. https://www.bmj.com/tamiflu

[59] Malhotra, A. (2022a). Curing the pandemic of misinformation on COVID-19 mRNA vaccines through real evidence-based medicine - Part 1. Journal of Metabolic Health, 5(1), 8 pages. doi:https://doi.org/10.4102/jir.v5i1.71

[60] Malhotra, A. (2022b). Curing the pandemic of misinformation on COVID-19 mRNA vaccines through real evidence-based medicine - Part 2. Journal of Metabolic Health, 5(1), 10 pages. doi:https://doi.org/10.4102/jir.v5i1.72

Dr Aseem Malhotra MD

29th of November 2023

Covid-19: The illusion of efficacy and safety for vaccines and other interventions

Italian Medical-Scientific Independent Commission International Conference on Covid-19 management and the risks of the new W.H.O. binding policies

Italian Senate, Rome

19 April 2024

Norman Fenton

Overview

The definitions that shaped the narrative

The early ‘mortality by vaccination’ data

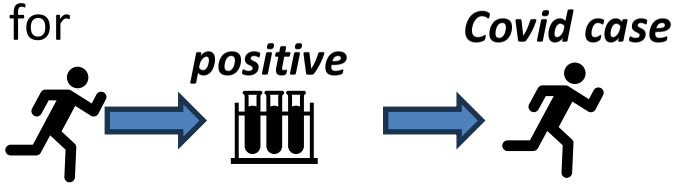
The ‘cheap trick’ illusion of vaccine effectiveness

The cheap trick in practice

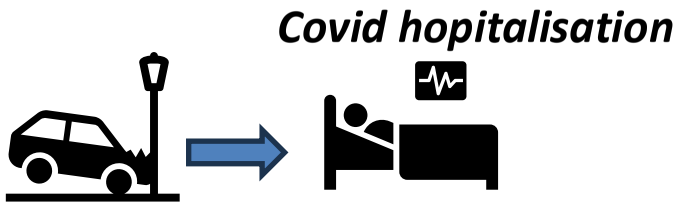
Conclusions and recommendations

The definitions that shaped the narrative

Fred, who has no Covid symptoms, tests positive in a PCR test for work.
He doesn't go on to develop any symptoms.
Fred is classified as a Covid case

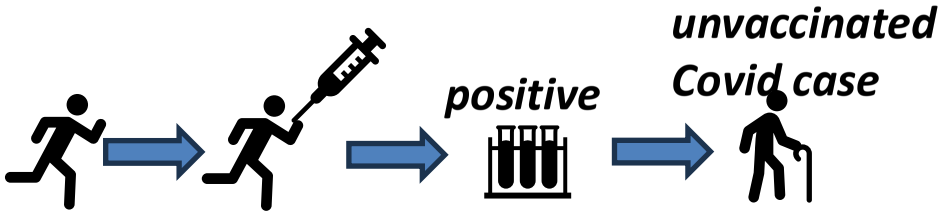


13 days after his PCR test Fred is critically injured in a car crash and rushed to hospital
Fred is classified as a Covid hospital admission

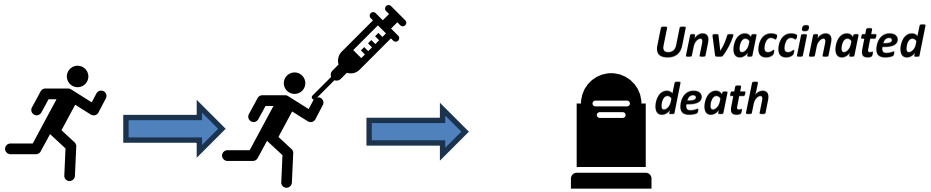


2 weeks after being taken to hospital Fred dies from his injuries
Fred is classified as a Covid death

Jim is healthy, gets a Covid vaccine
13 days later tests PCR positive with symptomatic Covid
Jim is classified as an unvaccinated Covid case

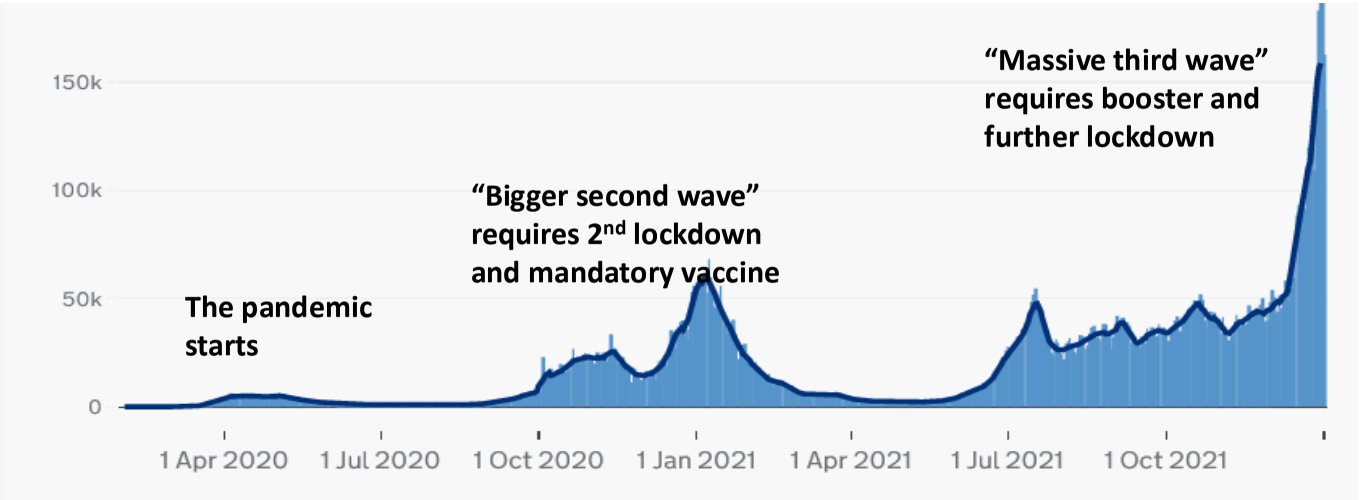


Peter is healthy, gets a Covid vaccine
dies the next day
Peter is classified as an unvaccinated death



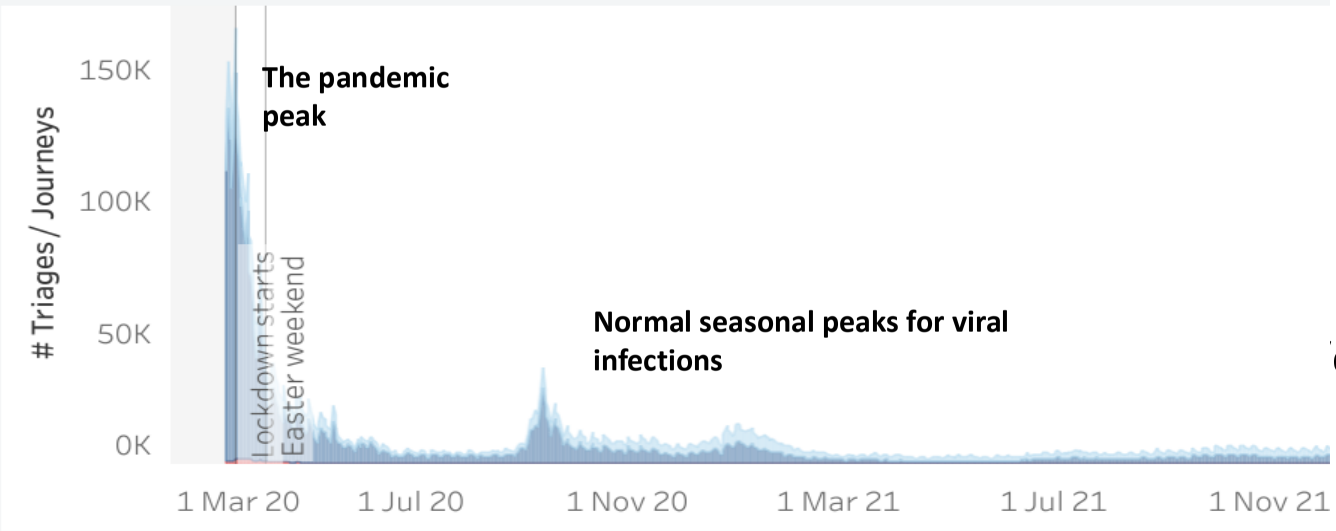
Were there really big second and third waves at the end of 2020 and 2021?

UK Covid daily 'Cases'



https://coronavirus.data.gov.uk/

UK daily Covid triage calls (online, 111 and 999 ambulance)



digital.nhs.uk/dashboards/nhs-pathways

The early ‘mortality by vaccination’ data

Office for National Statistics

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census 2021 Data and analysis from Census 2021

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Deaths involving COVID-19 by vaccination status, England

Deaths involving COVID-19 by vaccination stat England: deaths occurring between 2 January 24 September 2021

Weekly age-standardised mortality rates and age-specific rates for deaths involving COVID-19 by vaccination status; deaths occurring between 2 January and 24 September 2021 in England.

Official mortality data for England suggest systematic miscategorisation of vaccine status and uncertain effectiveness of Covid-19 vaccination

January 2022

DOI: 10.13140/RG.2.2.28055.09124

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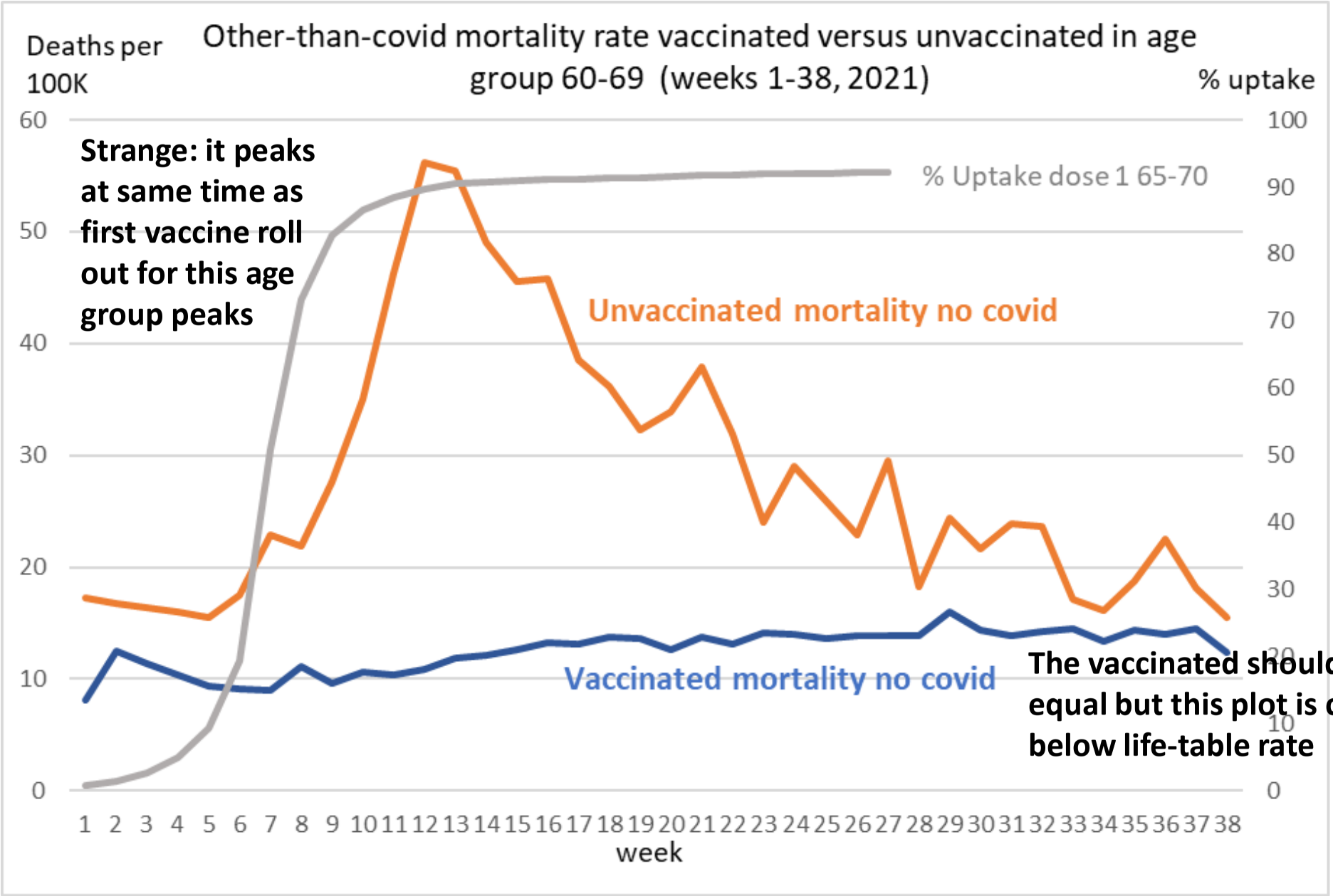
Lab: Norman Elliott Fenton's Lab

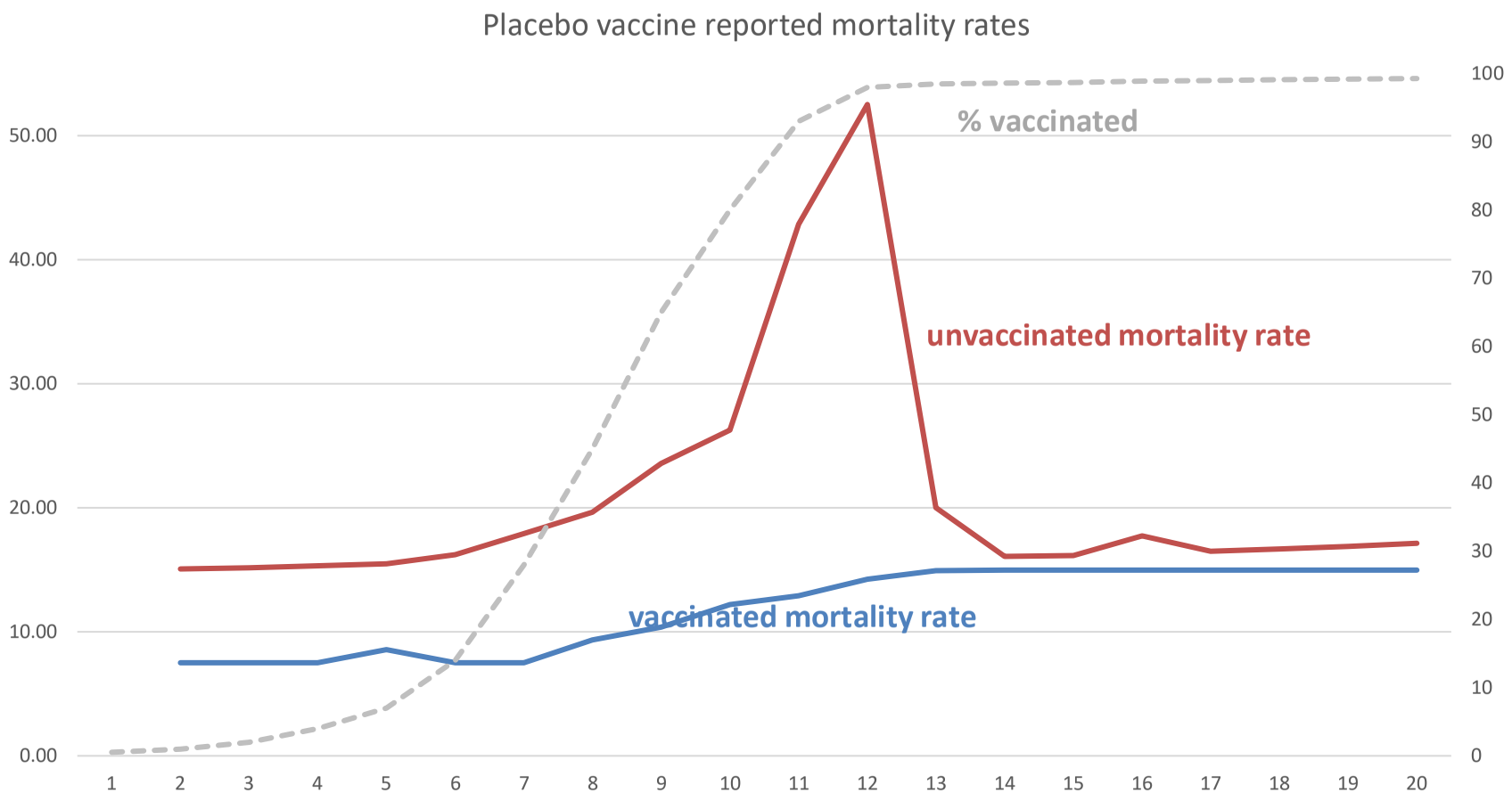
Martin Neil · Norman Elliott Fenton · Joel Smalley · Show all 9 authors · Jessica Rose

Martin Neil, Norman Fenton, Joel Smalley, Clare Craig, Joshua Guetzkow, Scott McLachlan, Jonathan Engler, Dan Russell and Jessica Rose

http://dx.doi.org/10.13140/RG.2.2.28055.09124


Other-than-covid mortality rate vaccinated versus unvaccinated in age group 60-69 (weeks 1-38, 2021)
Deaths per 100K
% uptake
Strange: it peaks at same time as first vaccine roll out for this age group peaks
% Uptake dose 1 65-70
Unvaccinated mortality no covid
Vaccinated mortality no covid
The vaccinated should be higher or equal but this plot is consistently below life-table rate
week

Placebo apparently saves lives….



The ‘cheap trick’ illusion of vaccine effectiveness

An extreme example: the worst possible vaccine

Everybody who gets the vaccine against diseases X gets infected with disease X within the first 14 days.

Then, assuming they don't get reinfected within say 12 weeks, we would record no cases of X in in those classified as 'vaccinated'.

Vaccine efficacy is defined as

$$1 - \left(\frac{\%\ \text{vaccinated who get X}}{\%\ \text{unvaccinated who get X}} \right) \text{as a percentage}$$

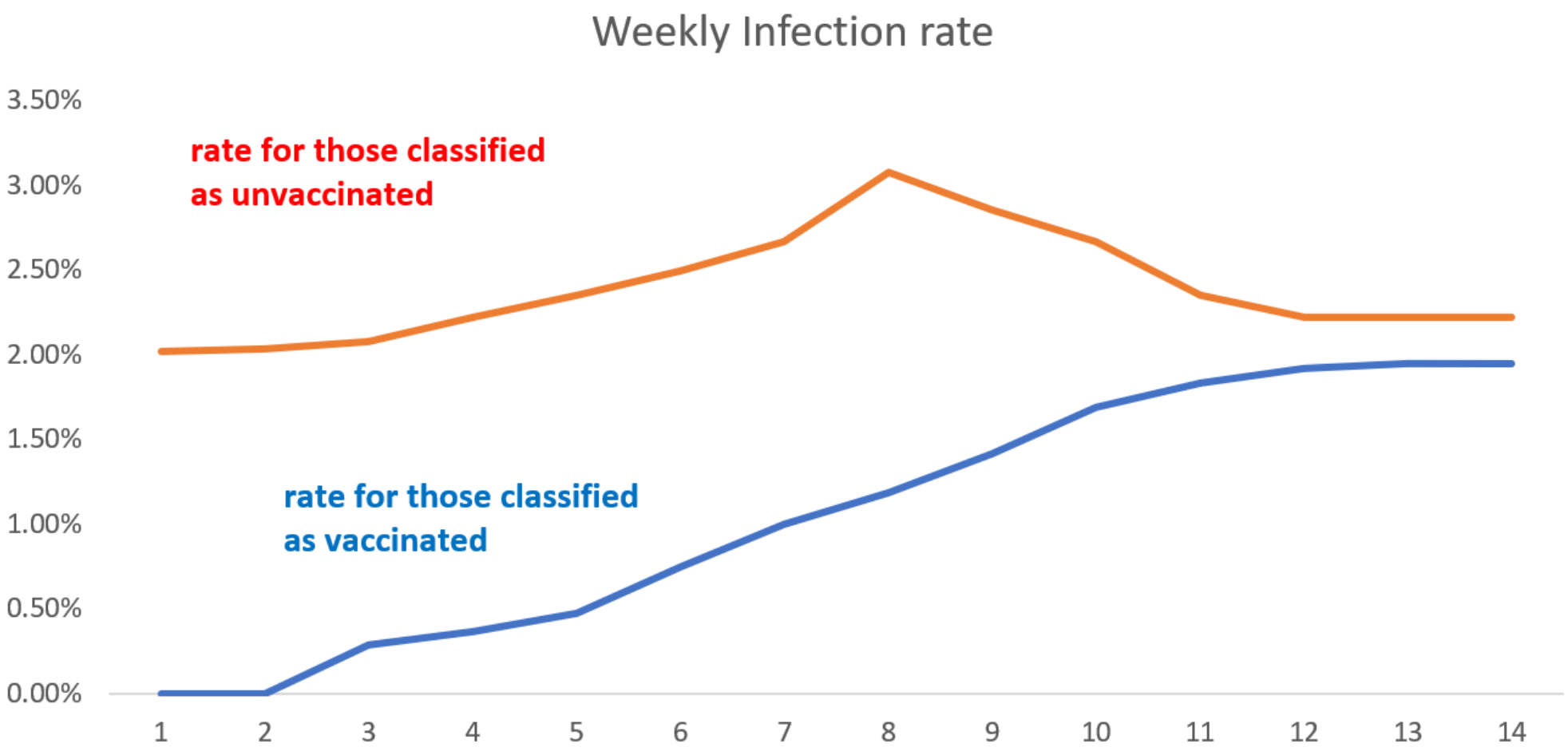
But,

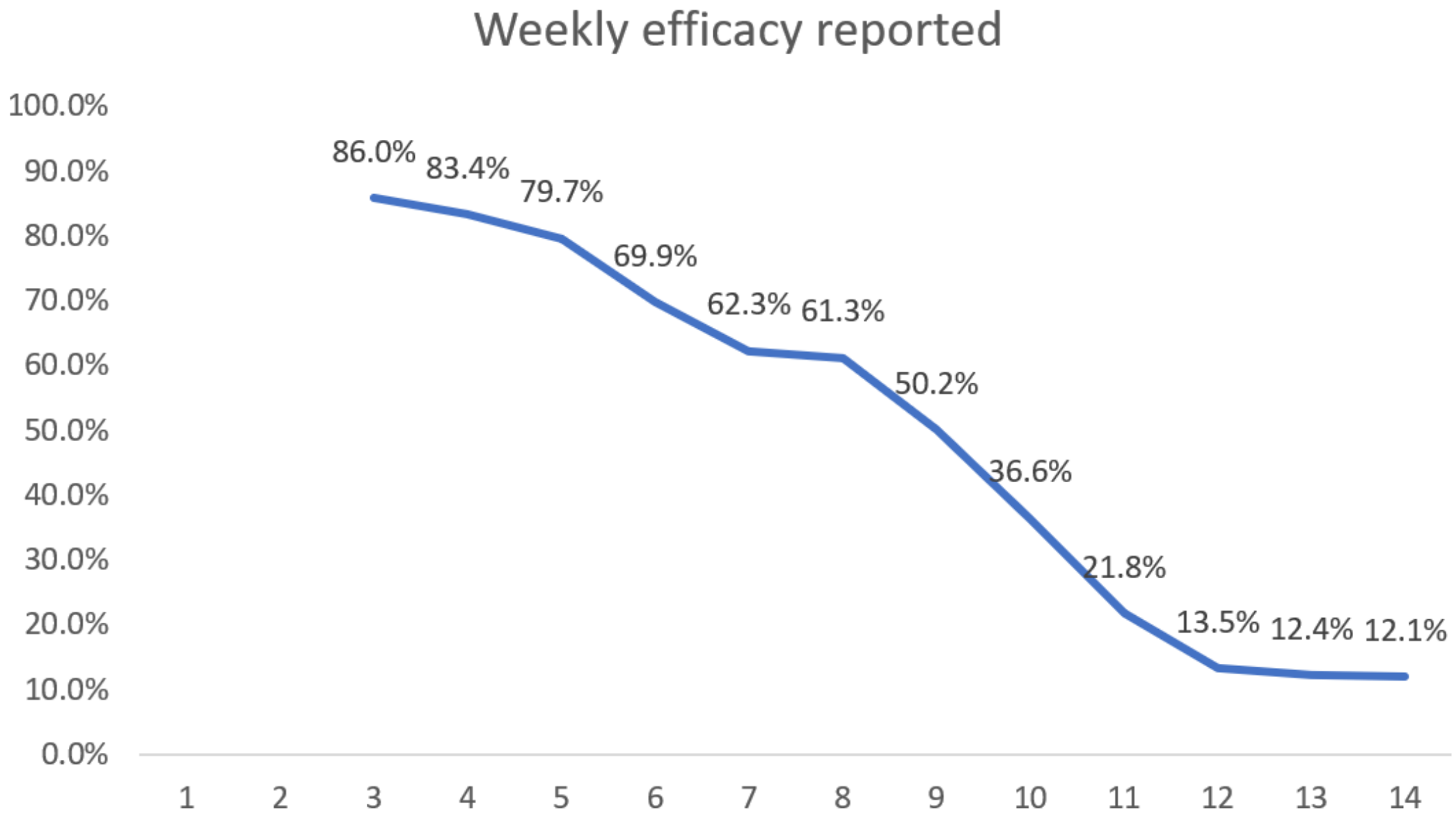
$$\%\ \text{vaccinated who get X} = 0$$

So, vaccine is 100% effective.

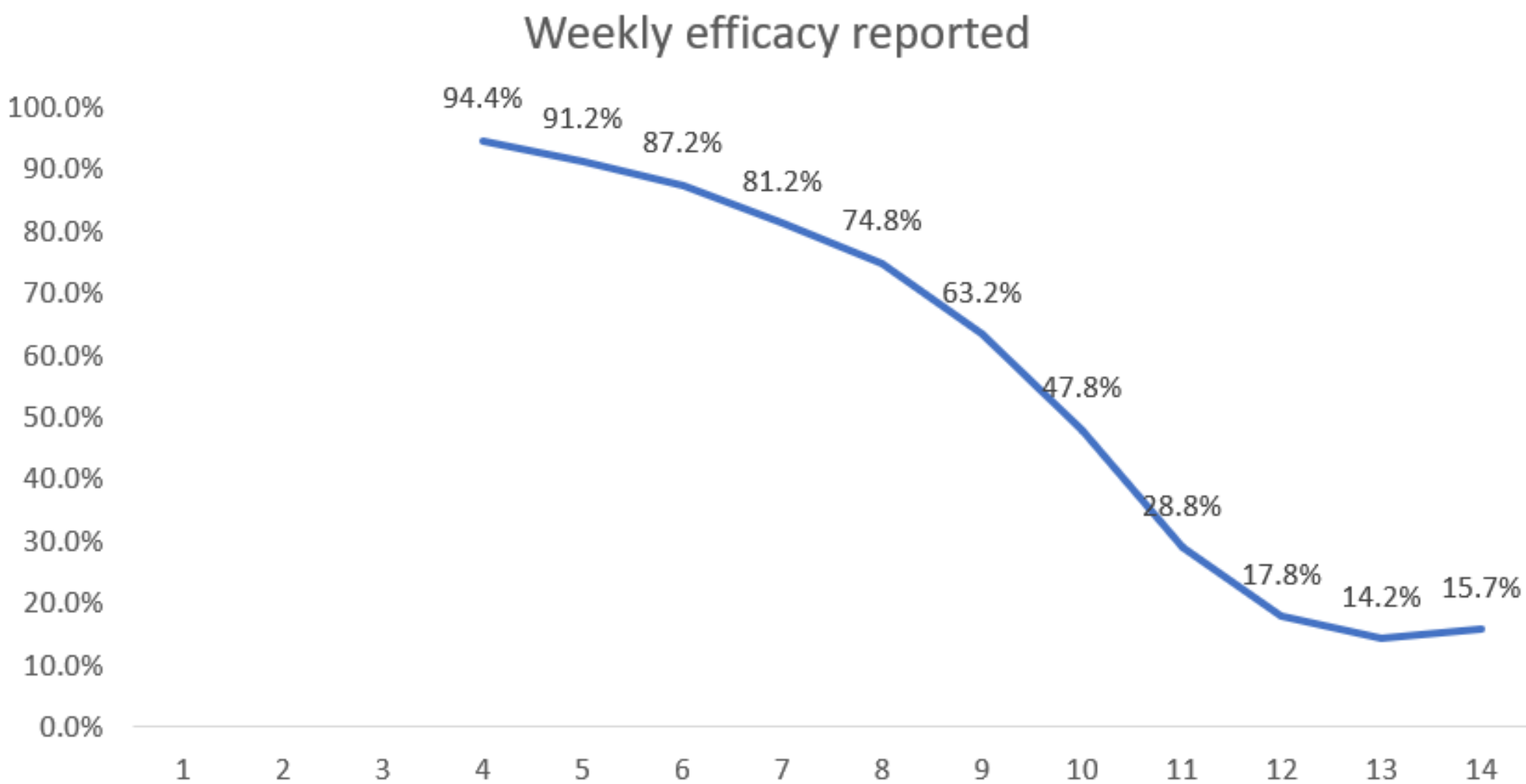
https://wherearethenumbers.substack.com/p/the-illusion-of-vaccine-efficacy

14-days rule




Weekly efficacy reported
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
86.0%
83.4%
79.7%
69.9%
62.3%
61.3%
50.2%
36.6%
21.8%
13.5%
12.4%
12.1%
1
2
3
4
5
6
7
8
9
10
11
12
13
14

21-day rule


Weekly efficacy reported
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
94.4%
91.2%
87.2%
81.2%
74.8%
63.2%
47.8%
28.8%
17.8%
14.2%
15.7%
1
2
3
4
5
6
7
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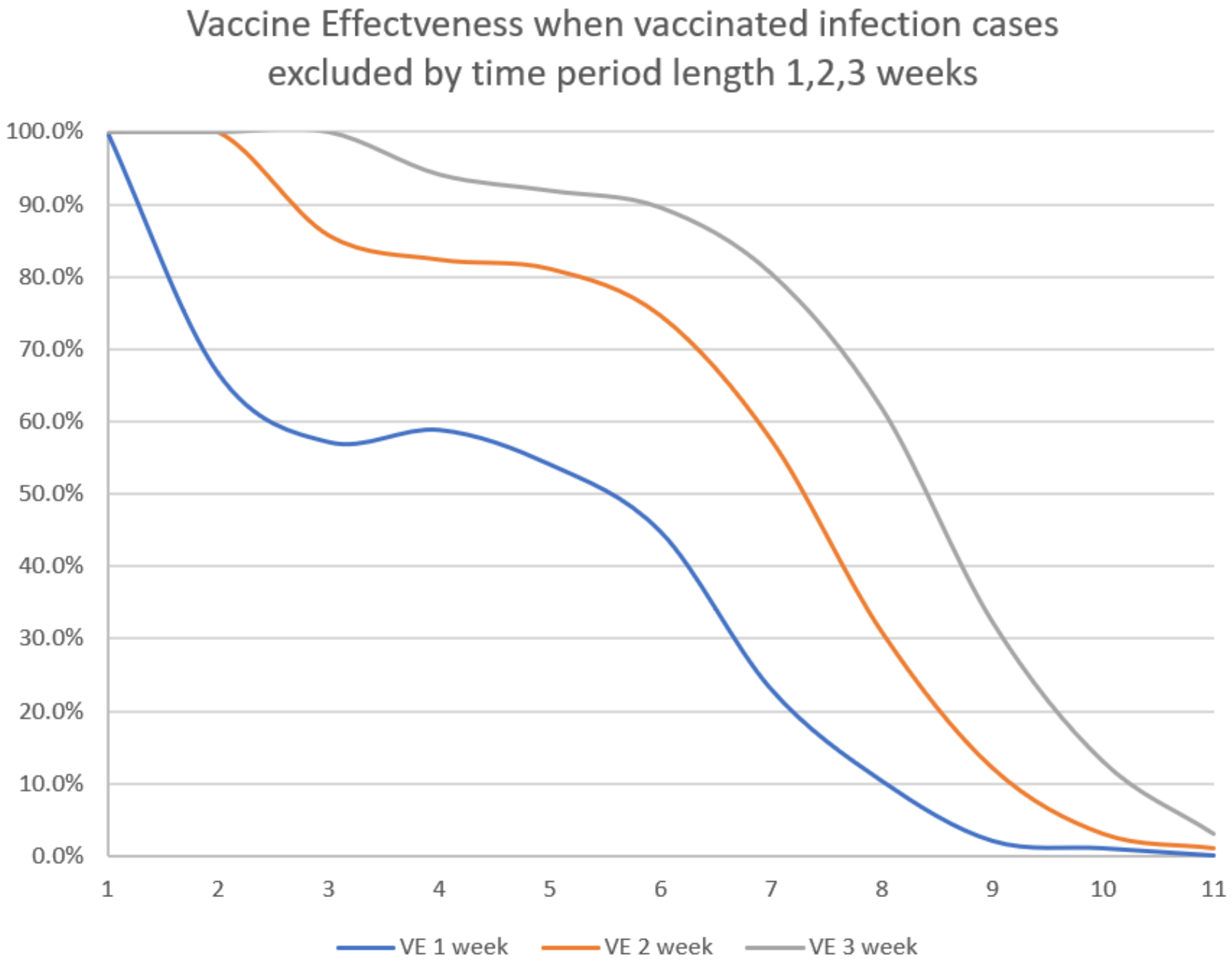
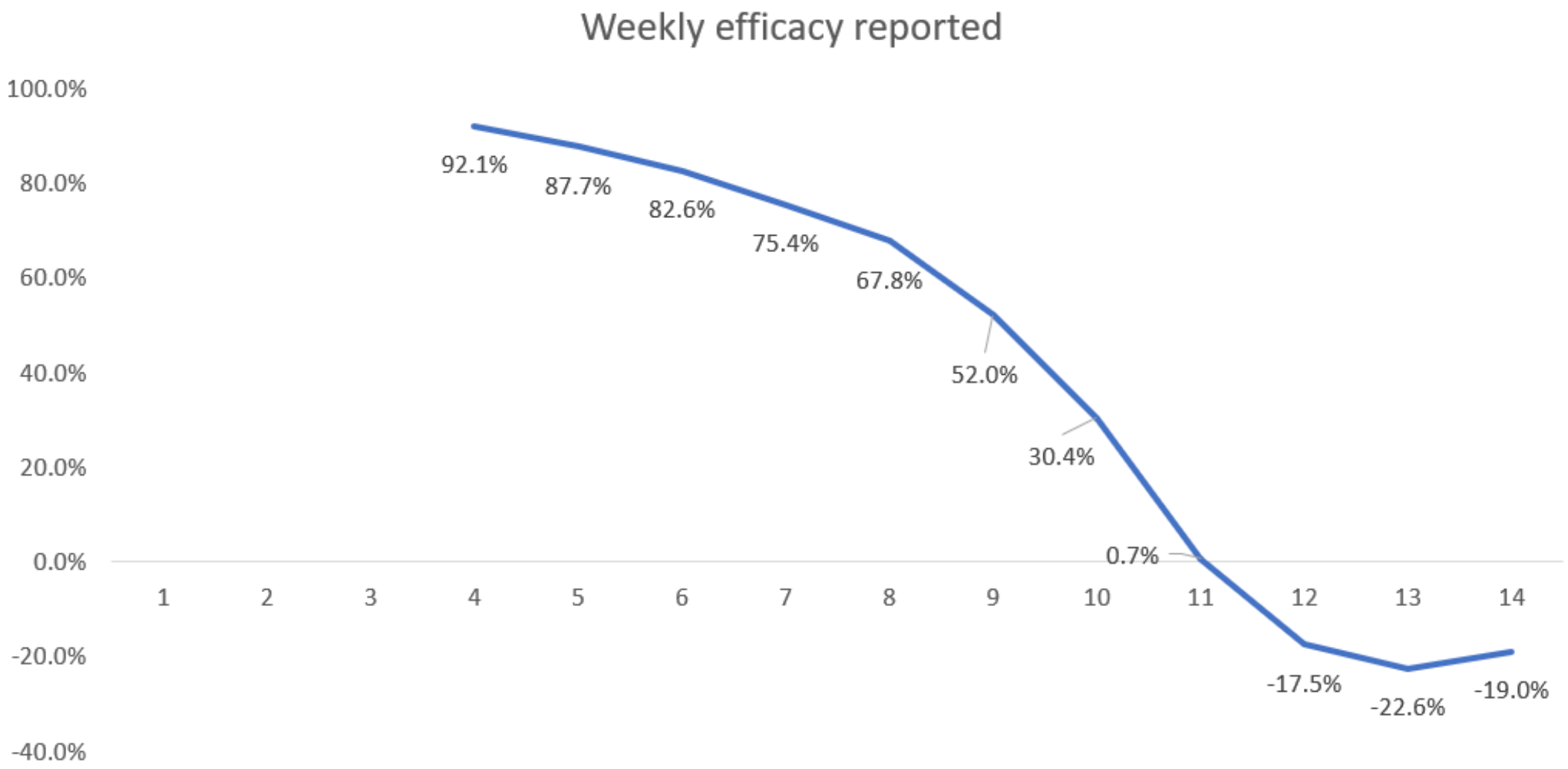
9
10
11
12
13
14

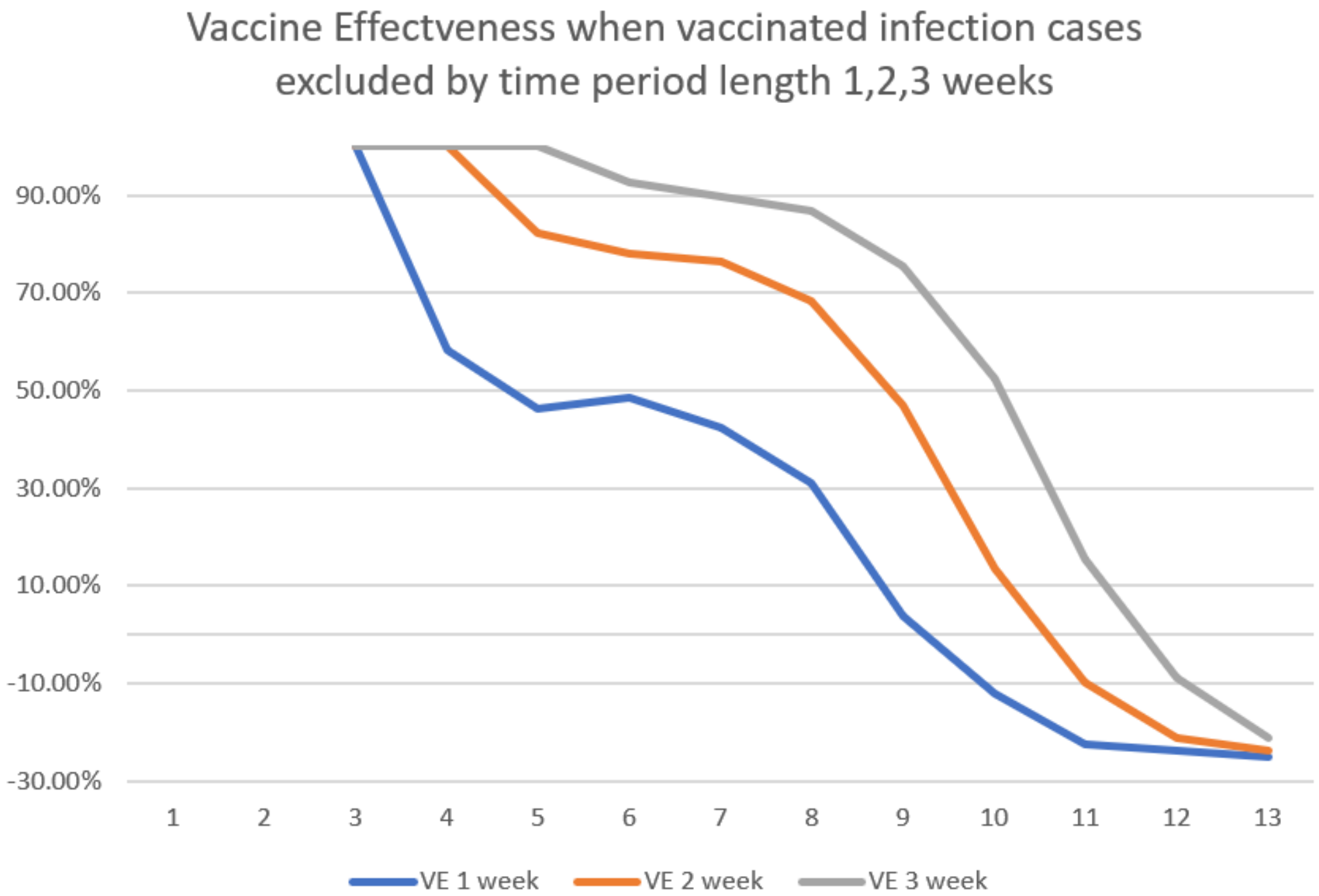

Vaccine Effectveness when vaccinated infection cases excluded by time period length 1,2,3 weeks
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
1
2
3
4
5
6
7
8
9
10
11
VE 1 week
VE 2 week
VE 3 week

Negative efficacy vaccine

Simulation when the vaccine induces a slightly high rate of infection (1.25%) than those unvaccinated (1%)

Assuming the 21 day delay period




Vaccine Effectveness when vaccinated infection cases excluded by time period length 1,2,3 weeks
90.00%
70.00%
50.00%
30.00%
10.00%
-10.00%
-30.00%
1
2
3
4
5
6
7
8
9
10
11
12
13
VE 1 week
VE 2 week
VE 3 week

The ‘cheap trick’ illusion in practice

ONS definition of who is ‘vaccinated’ for calculating vaccine efficacy

We calculated vaccine effectiveness for different doses (first, second and third dose or booster) and time since dose, to observe how the effectiveness changes over time. The vaccination statuses used were:

- unvaccinated (those with no vaccination or who were vaccinated with a first dose less than 21 days ago)
- first dose (those who were vaccinated with a first dose at least 21 days ago to earliest of less than 91 days after first dose or less than 21 days after second dose)

https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/covid19vaccineeffectivenessestimatedusingcensus2021variables
england/31march2021to20march2022

https://www.health.nsw.gov.au/Infectious/covid-19/Documents/in-focus/covid-19-vaccination-case-surveillance-051121.pdf

IN FOCUS

Vaccination among COVID-19 cases in the NSW Delta outbreak
Reporting period: 16 June to 7 October 2021

Methods

All individuals with locally-acquired confirmed SARS-CoV-2 infection, reported in the NSW Notifiable Conditions Information Management System (NCIMS) referred to here as 'COVID-19 cases' to 8pm on 7 October 2021 with a disease onset date from 16 June 2021 were extracted.

Vaccination status was initially determined based on what was reported in NCIMS (this information is collected at interview or on case review by the public health response teams). Vaccination data was then enhanced by matching to an extract of vaccination status from the Australian Immunisation Register (AIR). The AIR data was extracted on 7 October 2021 and included all people who were NSW residents and had any record of a COVID-19 vaccine. Individuals from the AIR extract were matched to NCIMS cases using an exact match on first name, last name and date of birth. If there were data on vaccination from both sources, AIR data was used as the source of information for analysis. Where data on vaccination existed in one system only, data from that system was used, if it was sufficiently complete. In the analyses, vaccination status was classified based on the following definitions:

- **None**: Reported as either: a) no vaccine record in NCIMS and unable to link to a record of any COVID-19 vaccination in AIR, or b) interval from receipt of first vaccine dose was too short to be effective (<21 days);
- **One**: One dose of vaccine at least 21 days prior to onset date;
- **Two**: Two doses of vaccine with the second dose at least 14 days prior to diagnosis and a minimum of 14 days between the two doses;
- **Unknown**: Information on vaccination (or vaccination date) unknown in NCIMS and unable to link to an AIR record of COVID-19 vaccination.

For analyses of rates of infections (described below) the group who had received one dose of vaccine, but the interval from vaccine receipt to case diagnosis was too short to be effective (<21 days), were classified separately from those not vaccinated.

The rate of infections amongst vaccinated and unvaccinated populations was estimated in fortnightly intervals since the outbreak began (to 30 June, 14 July, 28 July, 11 August, 25 August, 8 September, 22 September and 6 October) and by age group. For this estimate, the population was restricted to those aged 12 years and older and resident in the Greater Sydney region based on Statistical Local Area. Vaccination coverage data were extracted at the median date in each fortnightly interval. Rates of infection in the unvaccinated population were estimated by dividing the number of confirmed cases who had not received a COVID-19 vaccine, or who had unknown vaccination status, by the number of individuals in AIR reported with no doses in each interval. People with unknown vaccination status were included in the no vaccine category following a detailed review of the AIR records of a sample (see below). Rates of infection in those with 2 doses of COVID-19 vaccine were estimated in a similar manner although taking into account a 14-day interval since receipt of dose 2 of the vaccine for it to be effective.

To determine the presence of comorbidities or residence in aged care among COVID-19 cases who were admitted to ICU or died and had two doses of vaccine, health records were manually reviewed.

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The extent and impact of vaccine status miscategorisation on covid-19 vaccine efficacy studies

Martin Neil, Norman Fenton, Scott McLachlan

doi: https://doi.org/10.1101/2024.03.09.24304015

This article is a preprint and has not been certified by peer review [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.

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Abstract | Full Text | Info/History | Metrics | Preview PDF

Abstract

It is recognised that many studies reporting high efficacy for Covid-19 vaccines suffer from various selection biases. Systematic review identified thirty-eight studies that suffered from one particular and serious form of bias called miscategorisation bias, whereby study participants who have been vaccinated are categorised as unvaccinated up to and until some arbitrarily defined time after vaccination occurred. Simulation demonstrates that this miscategorisation bias artificially boosts vaccine efficacy and infection rates even when a vaccine has zero or negative efficacy. Furthermore, simulation demonstrates that repeated boosters, given every few months, are needed to maintain this misleading impression of efficacy. Given this, any claims of Covid-19 vaccine efficacy based on these studies are likely to be a statistical illusion.

https://doi.org/10.1101/2024.03.09.24304015

Systematic Review

Searched the 2 main literature Databases: PubMed and Scopus

Initial search returned over 2200 of which nearly 500 were duplicates.

Removed duplicates and looked at abstracts to see whether the paper described a novel trial

Only 34 presented a relevant novel study of vaccine efficacy or safety

A further 4 papers were identified through citation mining of included papers

These 38 include all the key well cited studies

Findings

Every one of the 38 papers involved the miscategorisation selection bias (delay of at least 7 days).

Also found other categories of selection bias:

- **Excluded**: Participants who are vaccinated but who become infected or died during the arbitrarily defined period are neither categorised as unvaccinated or vaccinated but are instead simply removed from analysis
- **Unverified**: Participants whose vaccination status is unknown or unverified are categorised as unvaccinated
- **Uncontrolled**: Participants are allowed to self-administer or self-report their vaccination or infection status, became unblinded or sought vaccination outside the study
- **Undefined**: The authors of the study fail to provide definitions for either or both vaccinated and unvaccinated cohorts

Research studies containing miscategorisation selection bias

Citation	(a)	(b)	(c)	(d)	(e)	Defined Period
Dagan et al (2021)	X					14 days
Haas et al (2021)	X					7 days
Rosenberg et al (2021)	X	X				14 days
Thomas et al (2021)	X					7 days
Angel et al (2021)	X		X			7 days
NSW Health (2021)	X	X				14 days
Ali et al (2021)	X					14 days
Pilishvili et al (2021)	X		X			14 days / 7 days
Andrews et al (2022)	X					28 days
Buam et al (2022)	X					21 days / 14 days
Buchan et al (2022)	X					7 days
Carazo et al (2022)	X					14 days
Chung et al (2022)	X					7 days
Palinkas et al (2022)	X					7 days
Ferdinands et al (2022)	X	X		X		14 days
Lyngse et al (2022)	X					7-15 days
Lyngse et al (2022b)	X	X				7-15 days
Nordstrom et al (2022)	X			X	X	14 days
Petras et al (2022)	X					14 days
Robles-Fontan et al (2022)	X					14 days
Arbel et al (2022)	X					7 days
Paternina et al (2022)	X					14 days
Stock et al (2022)	X					21 days / 14 days
Bermingham et al (2023)	X					21 days
Yau et al (2023)	X					Until fully vaccinated
Mitchell et al (2023)	X					14 days
Tan et al (2023)	X					7 days
Al Kaabi et al (2023)	X					14 days
Tabarsi et al (2023)	X		X	X		14 days
Heath et al (2023)	X		X			7 days
Nadeem et al (2023)	X					14 days
Anez et al (2023)	X					7 days
Munoz et al (2023)	X					7 days
Wu et al (2023)	X		X			28 days
Bermingham et al (2023b)	X				X	21 days
Liu et al (2023)	X					7 days
Kitano et al (2023)	X					7 days / 14 days
Polack et al (2020)	X			X		7 days
Khairullin et al (2022)	X					14 days
	39	4	5	4	2	

nature communications

Article | Open Access | Published: 30 September 2022

Household transmission of SARS-CoV-2 Omicron variant of concern subvariants BA.1 and BA.2 in Denmark

Frederik Plesner Lyngse, Carsten Thure Kirkeby, Matthew Denwood, Lasse Engbo Christiansen, Kåre Mølbak, Camilla Holten Møller, Robert Leo Skov, Tyra Grove Krause, Morten Rasmussen, Raphael Niklaus Sieber, Thor Bech Johannesen, Troels Lillebaek, Jannik Fonager, Anders Fomsgaard, Frederik Trier Møller, Marc Stegger, Maria Overvad, Katja Spiess & Laust Hvas Mortensen

Nat

730

[a]Unvaccinated includes individuals with partial vaccination (24 primary cases and 18 contacts). [b]Fully vaccinated includes unvaccinated individuals with previous infection.

Abstract

SARS coronavirus 2 (SARS-CoV-2) continues to evolve and new variants emerge. Using nationwide Danish data, we estimate the transmission dynamics of SARS-CoV-2 Omicron subvariants BA.1 and BA.2 within households. Among 22,678 primary cases, we identified 17,319 secondary infections among 50,588 household contacts during a 1–7 day follow-up. The secondary attack rate (SAR) was 29% and 39% in households infected with Omicron BA.1 and BA.2, respectively. BA.2 was associated with increased susceptibility of infection for unvaccinated household contacts (Odds Ratio (OR) 1.99; 95%–CI 1.72-2.31), fully vaccinated contacts (OR 2.26; 95%–CI 1.95–2.62) and booster-vaccinated contacts (OR 2.65; 95%–CI 2.29–3.08), compared to BA.1. We also found increased infectiousness from unvaccinated primary cases infected with BA.2 compared to BA.1 (OR 2.47; 95%–CI 2.15–2.84), but not for fully vaccinated (OR 0.66; 95%–CI 0.57–0.78) or booster-vaccinated primary cases (OR 0.69; 95%–CI 0.59–0.82). Omicron BA.2 is inherently more transmissible than BA.1. Its immune-evasive properties also reduce the protective effect of vaccination against infection, but do not increase infectiousness of breakthrough infections from vaccinated individuals.

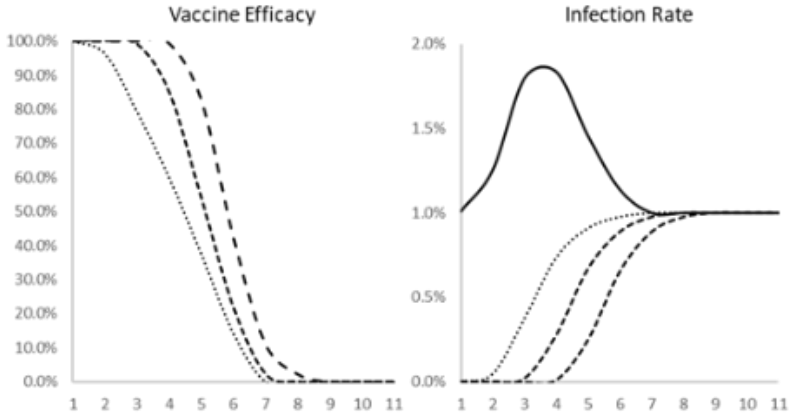
Table 1 Summary Statistics (primary cases and contacts reported separately)

From: Household transmission of SARS-CoV-2 Omicron variant of concern subvariants BA.1 and BA.2 in Denmark

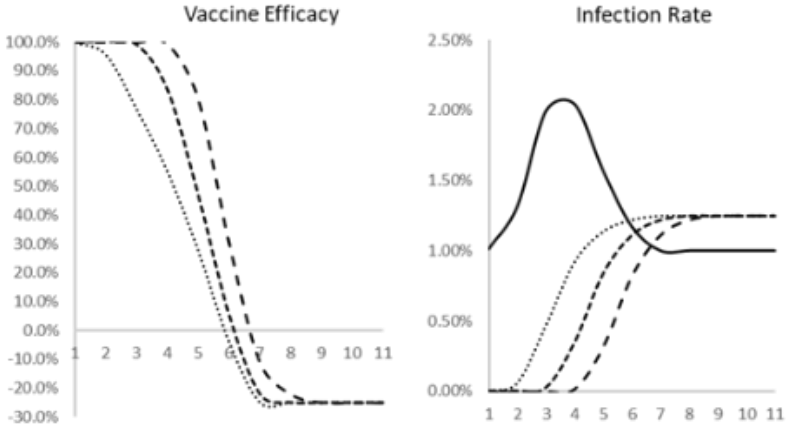
	Omicron - BA.2				Omicron - BA.1			
	Primary cases	Household contacts	Secondary cases	SAR (%)	Primary cases	Household contacts	Secondary cases	SAR (%)
Total	11,348	25,859	10,102	39	11,330	24,729	7217	29
Sex								
Male	5504	13,040	4778	37	5487	12,450	3454	28
Female	5844	12,819	5324	42	5843	12,279	3763	31
Age								
0–9 years	2018	4922	1946	40	1123	4619	1457	32
								27
								29
								42
								27
								21
60–69 years	477	864	296	34	520	913	230	25
70+ years	279	414	144	35	300	439	122	28
Household size								
2 persons	3675	3675	1529	42	4087	4087	1278	31
3 persons	2674	5348	1961	37	2756	5512	1491	27
4 persons	3438	10,314	4180	41	3053	9159	2830	31
5 persons	1283		1975	38	1199	4796	1329	28
6 persons	278	1390	457	33	235	1175	289	25
Vaccination status								
Unvaccinated[a]	3285	6837	2839	42	2497	6683	2240	34
Fully vaccinated[b]	4667	7975	3293	41	5844	9458	2949	31
Booster vaccinated	3396	11,047	3970	36	2989	8588	2028	24

[a]Unvaccinated includes individuals with partial vaccination (24 primary cases and 18 contacts). [b]Fully vaccinated includes unvaccinated individuals with previous infection.

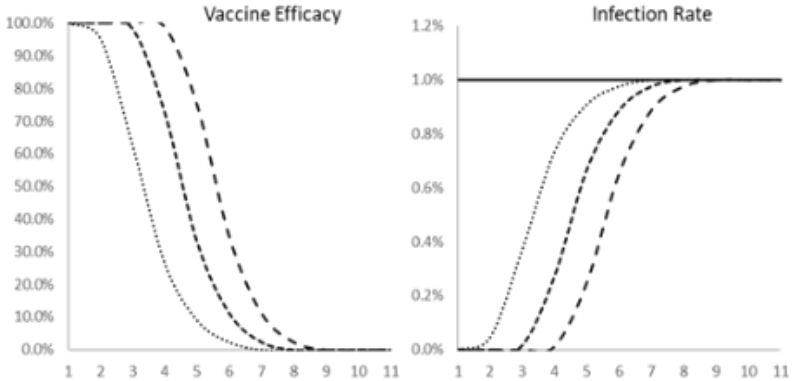
Simulations in our paper



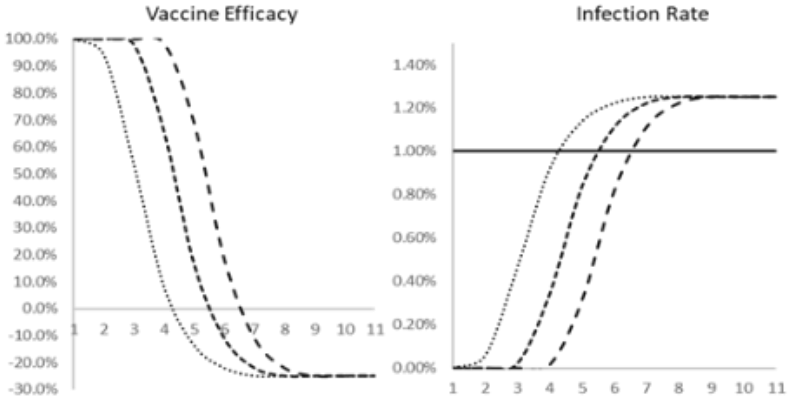
A. Miscategorisation, (a), with placebo vaccine



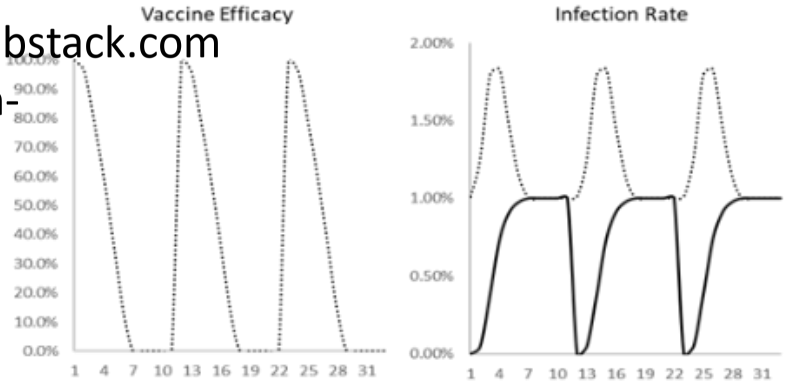
B. Miscategorisation, (a), with negative efficacy vaccine



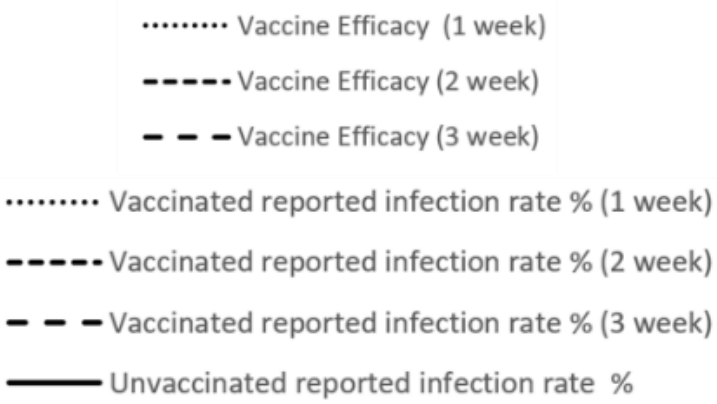
C. Exclusion, (c), with placebo vaccine



D. Exclusion, (c), with negative efficacy vaccine



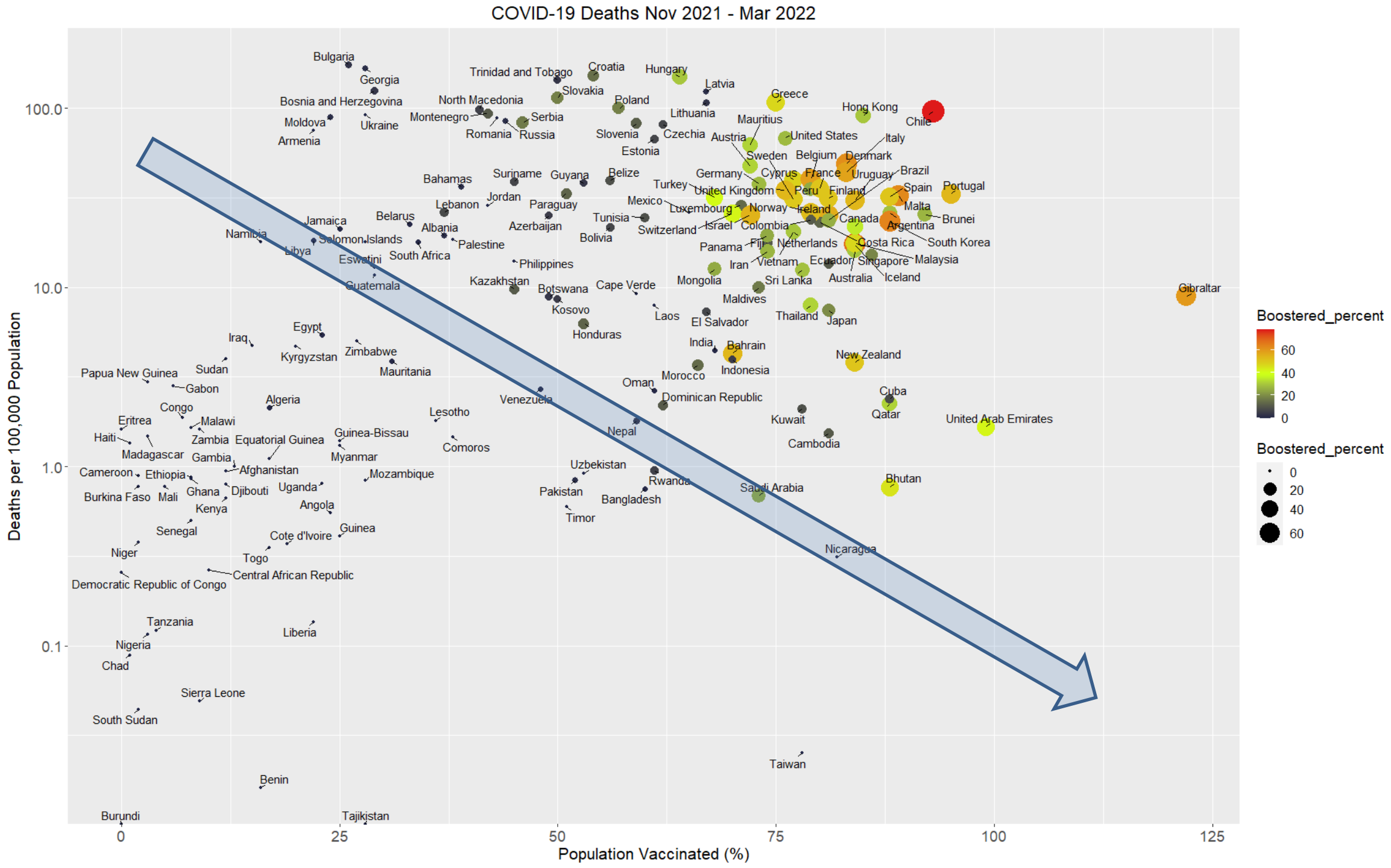
E. Boosting with miscategorisation, (a), with placebo vaccine



All available for download:

https://wherearethenumbers.substack.com/p/is-the-censorship-of-research-questioning

The failure of the vaccine and other interventions


COVID-19 Deaths Nov 2021 - Mar 2022
Deaths per 100,000 Population
Population Vaccinated (%)
100.0
10.0
1.0
0.1
0
25
50
75
100
125
Boostered_percent
60
40
20
0
Boostered_percent
0
20
40
60
Bulgaria
Georgia
Bosnia and Herzegovina
Moldova
Ukraine
Armenia
Trinidad and Tobago
Croatia
Hungary
Latvia
Slovakia
North Macedonia
Poland
Greece
Montenegro
Serbia
Romania
Russia
Lithuania
Mauritius
Hong Kong
Chile
Slovenia
Czechia
Austria
United States
Italy
Estonia
Sweden
Belgium
Denmark
Bahamas
Suriname
Guyana
Belize
Germany
Cyprus
France
Uruguay
Brazil
Turkey
United Kingdom
Peru
Finland
Spain
Portugal
Lebanon
Jordan
Paraguay
Mexico
Luxembourg
Norway
Ireland
Malta
Jamaica
Belarus
Tunisia
Canada
Brunei
Namibia
Albania
Azerbaijan
Switzerland
Israel
Colombia
Argentina
Solomon Islands
Palestine
Bolivia
Panama
Fiji
Netherlands
Costa Rica
South Korea
Libya
Eswatini
South Africa
Philippines
Iran
Vietnam
Ecuador
Singapore
Malaysia
Guatemala
Kazakhstan
Botswana
Cape Verde
Mongolia
Sri Lanka
Australia
Iceland
Gibraltar
Kosovo
Maldives
Laos
El Salvador
Thailand
Japan
Honduras
Egypt
Iraq
India
Bahrain
Kyrgyzstan
Zimbabwe
New Zealand
Papua New Guinea
Sudan
Mauritania
Morocco
Indonesia
Gabon
Oman
Cuba
Algeria
Venezuela
Dominican Republic
Congo
Lesotho
Qatar
Eritrea
Malawi
Kuwait
United Arab Emirates
Haiti
Zambia
Equatorial Guinea
Guinea-Bissau
Nepal
Madagascar
Comoros
Cambodia
Gambia
Myanmar
Cameroon
Ethiopia
Afghanistan
Uzbekistan
Mozambique
Rwanda
Bhutan
Burkina Faso
Mali
Ghana
Djibouti
Uganda
Pakistan
Saudi Arabia
Kenya
Angola
Bangladesh
Timor
Senegal
Cote d'Ivoire
Guinea
Niger
Togo
Nicaragua
Central African Republic
Democratic Republic of Congo
Tanzania
Liberia
Nigeria
Chad
Sierra Leone
South Sudan
Taiwan
Benin
Burundi
Tajikistan

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Clinical Medicine

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Article

Influence of Seasonality and Public-Health Interventions on the COVID-19 Pandemic in Northern Europe

Gerry A. Quinn [1,*], Michael Connolly [2], Norman E. Fenton [3], Steven J. Hatfill [4], Paul Hynds [5,6], Coilín ÓhAiseadha [5,7], Karol Sikora [8], Willie Soon [9,10] and Ronan Connolly [2,10]

1 Centre for Molecular Biosciences, Ulster University, Coleraine BT52 1SA, UK
2 Independent Researcher, D08 Dublin, Ireland
3 School of Electronic Engineering and Computer Science, Queen Mary University of London, London E1 4NS, UK
4 London Center for Policy Research, New York, NY 10004, USA
5 Spatiotemporal Environmental Epidemiology Research (STEER) Group, Environmental Sustainability & Health Institute, Technological University Dublin, D07 H6K8 Dublin, Ireland
6 Irish Centre for Research in Applied Geoscience, University College Dublin, D04 F438 Dublin, Ireland
7 Department of Public Health, Health Service Executive, Dr Steevens' Hospital, D08 W2A8 Dublin, Ireland
8 Department of Medicine, University of Buckingham Medical School, Buckingham MK18 1EG, UK
9 Institute of Earth Physics and Space Science (ELKH EPSS), H-9400 Sopron, Hungary
10 Center for Environmental Research and Earth Sciences (CERES), Salem, MA 01970, USA
* Correspondence: g.quinn@ulster.ac.uk

Abstract: Background: Most government efforts to control the COVID-19 pandemic revolved around non-pharmaceutical interventions (NPIs) and vaccination. However, many respiratory diseases show distinctive seasonal trends. In this manuscript, we examined the contribution of these three factors to the progression of the COVID-19 pandemic. Methods: Pearson correlation coefficients and time-lagged analysis were used to examine the relationship between NPIs, vaccinations and seasonality (using the average incidence of endemic human beta-coronaviruses in Sweden over a 10-year period as a proxy) and the progression of the COVID-19 pandemic as tracked by deaths; cases; hospitalisations; intensive care unit occupancy and testing positivity rates in six Northern European countries (population 99.12 million) using a population-based, observational, ecological study method. Findings: The waves of the pandemic correlated well with the seasonality of human beta-coronaviruses (HCoV-OC-43 and HCoV-HKU-1). In contrast, we could not find clear or consistent evidence that the stringency of NPIs or vaccination reduced the progression of the pandemic. However, these results are correlations and not causations. Implications: We hypothesise that the apparent influence of NPIs and vaccines might instead be an effect of coronavirus seasonality. We suggest that policymakers consider these results when assessing policy options for future pandemics. Limitations: The study is limited to six temperate Northern European countries with spatial and temporal variations in metrics used to track the progression of the COVID-19 pandemic. Caution should be exercised when extrapolating these findings.

Keywords: COVID-19 pandemic; seasonal variation; public health; vaccination; epidemiology; Northern Europe

check for updates

Citation: Quinn, G.A.; Connolly, M.; Fenton, N.E.; Hatfill, S.J.; Hynds, P.; ÓhAiseadha, C.; Sikora, K.; Soon, W.; Connolly, R. Influence of Seasonality and Public-Health Interventions on the COVID-19 Pandemic in Northern Europe. *J. Clin. Med.* **2024**, *13*, 334. https://doi.org/10.3390/jcm13020334

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Table 1. Influence on progression of pandemic in terms of lagged deaths.

Northern European Countries	NPIs	Vaccination	Seasonality
Ireland	x	x	✓
UK	x	x	✓
Sweden	x	x	✓
Denmark	x	x	✓
Finland	x	x	✓
Norway	x	x	✓

✓ in green background indicates that a clear, consistent and physically plausible influence of the factor on the progression of the pandemic was identified for this country while x in red background indicates that an influence was not identified for this country.

Table 2. Influence on progression of pandemic in terms of cases.

Northern European Countries	NPIs	Vaccination	Seasonality
Ireland	x	x	✓
UK	x	x	✓
Sweden	x	x	✓
Denmark	x	x	✓
Finland	x	x	✓
Norway	x	x	✓

✓ in green background indicates that a clear, consistent and physically plausible influence of the factor on the progression of the pandemic was identified for this country while x in red background indicates that an influence was not identified for this country.

Conclusions and Recommendations

None of the ‘official data’ on covid ‘cases’, ‘hospitalisations’ and ‘deaths’ can be trusted. Much of it was geared towards framing a narrative of the need for a vaccine

All of the published empirical studies claiming vaccine efficacy and safety suffer from one or more types of misclassification bias

This type of misclassification will inevitably show even a useless vaccine as highly effective in the early weeks of a vaccine roll-out

Hence even if there were some genuine efficacy in the vaccines, the results claimed in the studies would be massively exaggerated.

Overwhelming anecdotal evidence from our everyday lives indicates that the vaccines were not effective.

Since, increasingly, unbiased evidence is showing that all-cause mortality in the vaccinated may well be higher than the unvaccinated in each age group, **we recommend that any further rollout of the covid vaccines should be terminated**

U.S. Department of Health and Human Services
HRSA
Health Resources and Services Administration

Updating the Vaccine Injury Table following the 2011 IOM Report on Adverse Effects of Vaccines

Rosemary Johann-Liang, M.D.
Chief Medical Officer, National Vaccine Injury Compensation Program (NVICP)

Advisory Commission on Childhood Vaccines, March 8, 2012

Objective: To seek advice and concurrence on the proposed changes to the NVICP's Vaccine Injury Table (VIT)

U.S. Department of Health and Human Services
HRSA
Health Resources and Services Administration

1) History and Overview
   - Reason for IOM Review on Vaccine Adverse Events (AE)
   - IOM Vaccine-AE Review History
   - IOM Committee Review Methods, Causality Framework, and Causality Conclusions
   - Preparation sequence: Proposals to update VIT and it's Qualifications & Aids to Interpretation (QAI)
   - Acknowledgements of the working group members of the HRSA/CDC Public Health Task Force

2) Legal and Policy implications in updating the VIT

3) Translation of IOM's causality conclusions to VIT Updates
   - Varicella Vaccine AE Additions (Dr. Catherine Shaer)
   - MMR Vaccine AE Additions (Dr. Mary Rubin)
   - Injection-Related AE Additions to multiple vaccines (Dr. Tom Ryan)
   - Anaphylaxis Additions to multiple vaccines (Dr. Sarah Atanasoff)
   - Additional proposals to change/add to the Aids to Interpretation (Dr. Stacy Stryer)
   - Additional items from Working Group deliberations (Dr. Tom Shimabukuro)

4) Next Steps and Project Timeline (Estimated)

IOM Vaccine - AE Review

- **Purpose**: Review the current medical and scientific evidence on vaccines and AEs in order to update the National Vaccine Injury Compensation Program's Vaccine Injury Table (VIT) and the Qualifications & Aids to Interpretation (QAI), thus providing provide the scientific basis for future review/adjudication of VICP claims.

- Congress created the original VIT in 1986 as a compromise mechanism allowing a legal presumption of causation for certain vaccines and conditions.

- Due to uncertainties over what injuries are vaccine-related, Congress called for IOM reviews of the scientific and medical literature on vaccine adverse events, and for the Secretary of HHS to modify the VIT once these findings were made available.

- Previous IOM reports on vaccines and adverse events in 1991 and 1994 led to rulemaking changes in 1995 and 1997.

- Since the last revision to the VIT in 1997, there have been 9 vaccines added to the program without any expert reviews or independent examination of the adverse events associated with the use of these vaccines.

History behind 2011 IOM Report

- Contract initiation September 2008; IOM Committee (15 members) convened.

- Charge to Committee April 2009: Independent review of the current epidemiological, clinical, and biologic literature (started with 4 vaccines).
  - Framework for categorizing the evidence of causality
  - Describe the strength of evidence regarding biological mechanisms underlying theories when evidence is not enough for causal conclusions
  - Develop a report on the evidence regarding AEs associated with vaccines

- Supplemental funding (all within HHS) through VICP/HRSA, NVPO/HHS and ISO/CDC in September 2009 allowed the addition of 4 more vaccines for review.

- Committee reviewed a total of 8 vaccines, constituting 12 of 16 vaccine antigen combinations found in 92% of VICP claims: Hep A, Hep B, human papillomavirus, influenza, meningococcal, MMR, tetanus-containing, and varicella.

Current Vaccines Listed in VIT

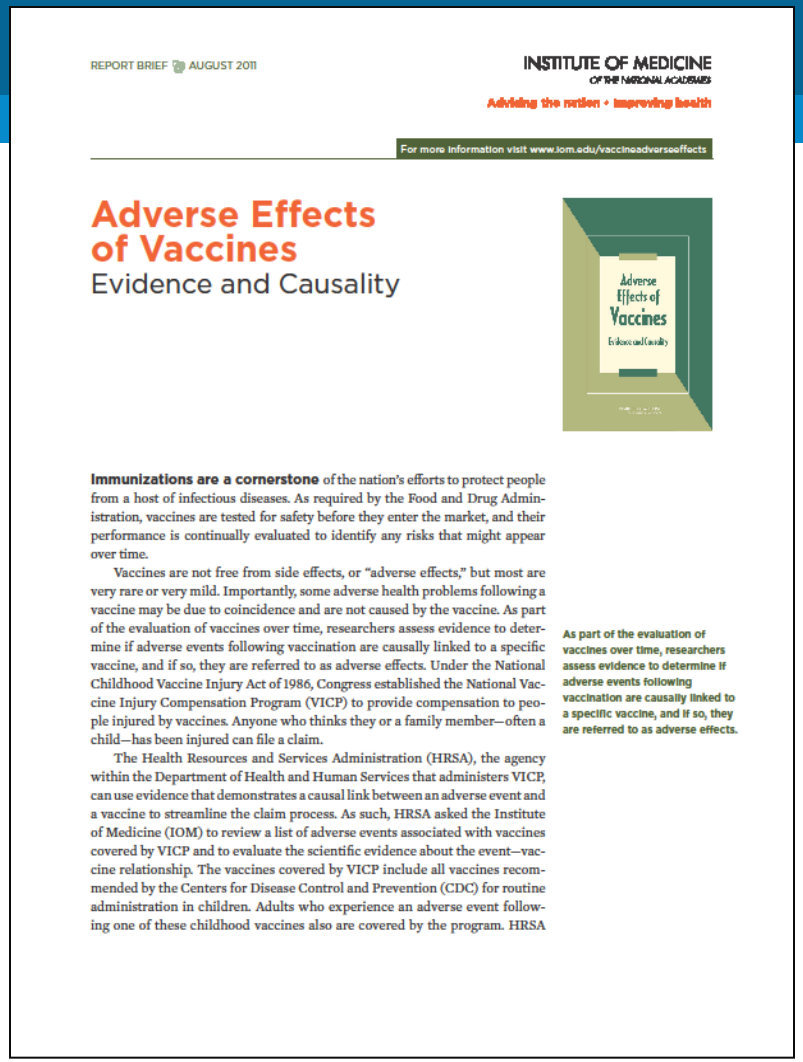
Last IOM-based revisions to the VIT-QAI was 1997 and covered the following vaccines

- Diphtheria, tetanus, pertussis (DTP, DTaP, DT, TT, or Td)
- Measles, mumps, rubella (MMR or any components)
- Polio (OPV or IPV)

Nine vaccines added to the VIT since last IOM review

- Hepatitis B vaccine
- *Haemophilus influenza* type b (Hib) vaccine
- Varicella virus vaccine
- Rotavirus vaccine
- Pneumococcal conjugate vaccine
- Hepatitis A vaccine
- Trivalent influenza vaccine
- Meningococcal vaccine
- Human papillomavirus vaccine

- Final report publically released 8/25/11
- Dr. Ellen Clayton (Committee Chair) briefed ACCV (9/1/11) and the National Vaccine Advisory Committee (9/13/11).



REPORT BRIEF AUGUST 2011

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES
Advising the nation • Improving health

For more information visit www.iom.edu/vaccineadverseeffects

Adverse Effects of Vaccines

Evidence and Causality

Immunizations are a cornerstone of the nation's efforts to protect people from a host of infectious diseases. As required by the Food and Drug Administration, vaccines are tested for safety before they enter the market, and their performance is continually evaluated to identify any risks that might appear over time.

Vaccines are not free from side effects, or "adverse effects," but most are very rare or very mild. Importantly, some adverse health problems following a vaccine may be due to coincidence and are not caused by the vaccine. As part of the evaluation of vaccines over time, researchers assess evidence to determine if adverse events following vaccination are causally linked to a specific vaccine, and if so, they are referred to as adverse effects. Under the National Childhood Vaccine Injury Act of 1986, Congress established the National Vaccine Injury Compensation Program (VICP) to provide compensation to people injured by vaccines. Anyone who thinks they or a family member—often a child—has been injured can file a claim.

The Health Resources and Services Administration (HRSA), the agency within the Department of Health and Human Services that administers VICP, can use evidence that demonstrates a causal link between an adverse event and a vaccine to streamline the claim process. As such, HRSA asked the Institute of Medicine (IOM) to review a list of adverse events associated with vaccines covered by VICP and to evaluate the scientific evidence about the event—vaccine relationship. The vaccines covered by VICP include all vaccines recommended by the Centers for Disease Control and Prevention (CDC) for routine administration in children. Adults who experience an adverse event following one of these childhood vaccines also are covered by the program. HRSA

As part of the evaluation of vaccines over time, researchers assess evidence to determine if adverse events following vaccination are causally linked to a specific vaccine, and if so, they are referred to as adverse effects.

http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx

There were no recommendations, only findings

Adverse Events Reviewed

- Working list of adverse events was generated by HRSA's Division of Vaccine Injury Compensation (DVIC) medical staff based on the alleged injury petitions to VICP and current science with input from Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) staff through the Health and Human Services Interagency working group.

- Public input sought through ACCV and the IOM project website. Working list was first posted on December 2009.

Committee to Review Adverse Effects of Vaccines
December 2009 Working List of Adverse Events to be Considered by the Committee

DTaP/Tetanus Containing Vaccines	Hepatitis A Vaccine	Meningococcal Vaccine	MMR Vaccine
• Anaphylaxis or Anaphylactic Shock	• Anaphylaxis or Anaphylactic Shock	• Anaphylaxis or Anaphylactic Shock	• Anaphylaxis or Anaphylactic Shock
• Arthropathy (Arthritis, Arthralgia)			• Arthropathy (Arthritis, Arthralgia)
• Autism*			• Autism*
• Autism Spectrum Disorders (ASD)/Pervasive Developmental Disorders (PDD)*			• Autism Spectrum Disorders (ASD)/Pervasive Developmental Disorders (PDD)*
• Ataxia			• Ataxia
• Bell's Palsy	• Bell's Palsy		
			• Brachial Neuritis
			• Chronic Fatigue Syndrome
		• Chronic Headaches	
• Chronic, Remitting Demyelinating Diseases: ▪ Chronic Inflammatory Disseminated Polyneuropathy ▪ Multiple Sclerosis	• Chronic, Remitting Demyelinating Diseases: ▪ Chronic Inflammatory Disseminated Polyneuropathy ▪ Multiple Sclerosis	• Chronic, Remitting Demyelinating Diseases: ▪ Chronic Inflammatory Disseminated Polyneuropathy ▪ Multiple Sclerosis	• Chronic, Remitting Demyelinating Diseases: ▪ Chronic Inflammatory Disseminated Polyneuropathy ▪ Multiple Sclerosis
• Chronic Urticaria			
• Complex Regional Pain Syndrome			• Complex Regional Pain Syndrome
• Convulsions: ▪ Febrile, Afebrile ▪ Infantile Spasms ▪ Myoclonic Epilepsy			• Convulsions: ▪ Febrile, Afebrile ▪ Infantile Spasms ▪ Myoclonic Epilepsy
• Encephalopathy/Encephalitis		• Encephalopathy/Encephalitis	• Encephalopathy/Encephalitis
• Fibromyalgia			• Fibromyalgia
			• Hearing Loss
	• Hepatitis (autoimmune)		• Hepatitis
• Immune Thrombocytopenic Purpura			
• Insulin-dependent Diabetes Mellitus			• Insulin-dependent Diabetes Mellitus
• Monophasic Demyelinating Diseases: ▪ Acute Disseminating Encephalomyelitis ▪ Guillain-Barré Syndrome ▪ Transverse Myelitis	• Monophasic Demyelinating Diseases: ▪ Acute Disseminating Encephalomyelitis ▪ Guillain-Barré Syndrome ▪ Transverse Myelitis	• Monophasic Demyelinating Diseases: ▪ Acute Disseminating Encephalomyelitis ▪ Guillain-Barré Syndrome ▪ Transverse Myelitis	• Monophasic Demyelinating Diseases: ▪ Acute Disseminating Encephalomyelitis ▪ Guillain-Barré Syndrome ▪ Transverse Myelitis
• Myocarditis			
• Opsoclonus Myoclonus Syndrome			• Opsoclonus Myoclonus Syndrome
• Optic Neuritis			
• Serum Sickness			
• Sudden Infant Death Syndrome (SIDS)			

Also see General Considerations on page 4.

* "Secondary" autism or autistic features arising from chronic encephalopathy, mitochondrial disorders and/or other underlying disorders will be considered by the Committee. For "Primary" autism, VICP has asked the IOM to consider the review of the medical literature post *Immunization Safety Review: Vaccines and Autism (2004)* report. In particular, VICP is interested in the Committee's review on more recent theories of "neuroinflammation" and "hyperarousal/overexcitation of the immune system via multiple simultaneous antigenic stimulation."

Committee to Review Adverse Effects of Vaccines
December 2009 Working List of Adverse Events to be Considered by the Committee

Hepatitis B Vaccine	Human Papilloma Virus Vaccine	Influenza Vaccine	Varicella Vaccine
	• Amyotrophic Lateral Sclerosis		
• Anaphylaxis or Anaphylactic Shock	• Anaphylaxis or Anaphylactic Shock	• Anaphylaxis or Anaphylactic Shock	• Anaphylaxis or Anaphylactic Shock
• Arthropathy (Arthritis, Arthralgia)	• Arthropathy (Arthritis, Arthralgia)	• Arthropathy (Arthritis, Arthralgia)	• Arthropathy (Arthritis, Arthralgia)
		• Asthma	
		• Bell's Palsy	
• Brachial Neuritis	• Brachial Neuritis	• Brachial Neuritis	
		• Cardiac: ▪ Myocardial Infarction ▪ Stroke ▪ Sudden Death	
			• Cerebellar Ataxia
• Chronic, Remitting Demyelinating Diseases: ▪ Chronic Inflammatory Disseminated Polyneuropathy ▪ Multiple Sclerosis ▪ Neuromyelitis Optica	• Chronic, Remitting Demyelinating Diseases: ▪ Chronic Inflammatory Disseminated Polyneuropathy ▪ Multiple Sclerosis ▪ Neuromyelitis Optica	• Chronic, Remitting Demyelinating Diseases: ▪ Chronic Inflammatory Disseminated Polyneuropathy ▪ Multiple Sclerosis ▪ Neuromyelitis Optica	
• Complex Regional Pain Syndrome		• Complex Regional Pain Syndrome	
• Convulsions: ▪ Febrile, Afebrile ▪ Infantile Spasms ▪ Myoclonic Epilepsy			• Convulsions: ▪ Febrile, Afebrile ▪ Infantile Spasms ▪ Myoclonic Epilepsy
			• Disseminating Oka VZV Infection (in the immunocompromised)
• Encephalopathy/Encephalitis		• Encephalopathy/Encephalitis	• Encephalopathy/Encephalitis
• Fibromyalgia		• Fibromyalgia	
			• Hepatitis
	• Hypercoagulable States		
• Insulin-dependent Diabetes Mellitus			
			• Meningitis
• Monophasic Demyelinating Diseases: ▪ Acute Disseminating Encephalomyelitis ▪ Guillain-Barré Syndrome ▪ Transverse Myelitis	• Monophasic Demyelinating Diseases: ▪ Acute Disseminating Encephalomyelitis ▪ Guillain-Barré Syndrome ▪ Transverse Myelitis	• Monophasic Demyelinating Diseases: ▪ Acute Disseminating Encephalomyelitis ▪ Guillain-Barré Syndrome ▪ Transverse Myelitis	• Monophasic Demyelinating Diseases: ▪ Acute Disseminating Encephalomyelitis ▪ Guillain-Barré Syndrome ▪ Transverse Myelitis
		• Oculorespiratory Syndrome	
			• Oka VZV Zoster
	• Pancreatitis		
			• Pneumonia
• Polyarteritis Nodosa		• Polyarteritis Nodosa	
		• Small Fiber Neuropathy	
	• Syncope		
• Systemic Lupus Erythematosus		• Systemic Lupus Erythematosus	
			• Thrombocytopenia
	• Thromboembolic Events		
• Vasculitis		• Vasculitis	

Also see General Considerations on page 4.

Footnote expansions - AE List

- * "Secondary" autism or autistic features arising from chronic encephalopathy, mitochondrial disorders and/or other underlying disorders will be considered by the Committee. For "Primary" autism, VICP has asked the IOM to consider the review of the medical literature post *Immunization Safety Review: Vaccines and Autism (2004) report. In particular, VICP is interested in the Committee's review on more recent theories of "neuroinflammation" and "hyperarousal/overexcitation of the immune system via multiple simultaneous antigenic stimulation."*

- General Considerations: In addition to the specific adverse events, the committee will review general considerations for the eight vaccines. General considerations include underlying (susceptible) populations, "immune dysfunction", **vaccine administration issues, anaphylaxis** and autoimmune diseases (time interval), and sequential vaccination issues.

Adverse Events Reviewed

- The IOM Committee added 10 of their own adverse events.
  - All-cause mortality and seizures: influenza vaccine
  - Optic neuritis: MMR , influenza, hepatitis B, and DTaP vaccines
  - Neuromyelitis optica: MMR vaccine
  - Erythema nodosum: hepatitis B vaccine
  - Stroke and small fiber neuropathy: varicella vaccine

- The final working list constituted a diverse array of adverse events numbering 76 different adverse events and 158 adverse event-vaccine combinations; included 3 adverse events in the general category of injection-related events.

IOM Committee Review Methods

- For each vaccine-AE relationship, IOM made 3 assessments
  1. Weight-of-Epidemiologic Evidence (4 levels = high, moderate, limited, and insufficient).
  2. Weight-of-Mechanistic Evidence (4 levels = strong, intermediate, weak, and lacking).
  3. Causality Assessment: overall assessment made from position of *neutrality* and moved from neutral position only when the combination of epidemiologic and mechanistic evidence suggested a more definitive assessment regarding causation.

- Four categories of causation evidence
  1. Convincingly supports a causal relationship
  2. Favors acceptance of a causal relationship
  3. Inadequate to accept or reject a causal relationship
  4. Favors rejection of a causal relationship

IOM Committee Review Methods

- Two types of evidence were used
  - Epidemiologic evidence from studies of populations
  - Mechanistic evidence derived primarily from biological and clinical studies in animals and humans

- For weight of evidence, IOM used a summary classification scheme that incorporated both the quality and quantity of the individual studies and the consistency of the group of studies in terms of direction of effect.

IOM Committee Review Methods

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  1. Weight-of-Epidemiologic Evidence (4 levels = high, moderate, limited, and insufficient).
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- Four categories of causation evidence
  1. Convincingly supports a causal relationship
  2. Favors acceptance of a causal relationship
  3. Inadequate to accept or reject a causal relationship
  4. Favors rejection of a causal relationship

Summary of Causality Conclusions

- Convincingly supports a causal relationship (14 AE/vaccine relationships)
  - Varicella vaccine
    - Disseminated Oka VZV without other organ involvement
    - Disseminated Oka VZV with subsequent infection resulting in pneumonia, meningitis, or hepatitis
    - Vaccine strain viral reactivation without other organ involvement,
    - Vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis
  - MMR vaccine
    - Measles inclusion body encephalitis
    - Febrile seizures
  - MMR, varicella, influenza, hepatitis B, tetanus-containing, and meningococcal vaccines
    - Anaphylaxis.
  - Injection-related (potential for any vaccine)
    - Syncope
    - Deltoid bursitis (what HRSA has termed Shoulder Injury Related to Vaccine Administration or SIRVA)

Summary of Causality Conclusions

- Favors acceptance of a causal relationship (4 AE and vaccine relationships)

  1. HPV and anaphylaxis
  2. MMR and transient arthralgia in female adults
  3. MMR and transient arthralgia in children
  4. Certain trivalent inactivated influenza vaccines used in Canada and oculorespiratory syndrome

Summary of Causality Conclusions

- Inadequate to accept or reject a causal relationship (135 AE/vaccine relationships – 85% of all relationships)
  - IOM states that "… inadequate to accept or reject …" means just that – inadequate
  - Found in the vast majority of IOM conclusions on causality
  - Included vaccines and demyelinating diseases; the most common alleged injuries currently being claimed to VICP

Summary of Causality Conclusions

- Favors rejection of a causal relationship (5 AE and vaccine relationships)

  1. MMR vaccine and type 1 diabetes
  2. DTaP vaccine and type 1 diabetes
  3. MMR vaccine and autism
  4. Trivalent inactivated influenza vaccine (TIV) and asthma/reactive airway disease episodes
  5. TIV and Bell's palsy.

Preparation Sequence: Working Groups

- Task Force consisting of members from the Immunization Safety Office (ISO)/CDC, Division of Vaccine Injury Compensation (DVIC)/HRSA, and Office of General Counsel (OGC)/HHS established in September 2011

- **Phase 1 – Science based only:** Nine VIT Update Work Groups (VITU-WGs; 1 for each vaccine and 1 for injection-related events) reviewed IOM Report + updated literature on all Vaccine-Adverse Effect (AE) combinations using a consistent approach (organizing Phase 1 worksheets).

  – Recommended 21 Vaccine-AE combinations to move to Phase 2 (in addition to IOM's conclusively supports and favors acceptance categories, few were from IOM's inadequate to accept or reject categories).

  – Phase 1 complete (November 2011)

Preparation sequence: Phase 2

MMR - Transient arthralgia women	CS
MMR - Transient arthralgia children	CS
MMR - Measles inclusion encephalitis	CS
MMR - Chronic Arthritis/arthropathy	I
MMR - Febrile Seizures	CS
VARICELLA VIRUS - Disseminated Oka VZV Without Other Organ Inv	CS
VARICELLA VIRUS - Disseminated Oka VZV with Other Organ Inv	
VARICELLA VIRUS - Vaccine Strain Viral Reactivation w/o Other Organ Inv	CS
VARICELLA VIRUS - Vaccine Strain Viral Reactivation with Other Organ Inv	
VARICELLA VIRUS - Anaphylaxis	CS
FLU - Seizures Febrile	I
FLU - Guillain-Barré Syndrome	I
FLU - Anaphylaxis	CS
FLU - Live Attenuated/Asthma Exacerbation	I
HEP A - Anaphylaxis	I
HUMAN PAPILLOMA - Anaphylaxis	FA
DTAP - Encephalitis and Encephalopathy	I
MENINGOCOCCAL - Anaphylaxis	CS
INJECTION-RELATED - Complex Regional Pain Syndrome	I
INJECTION RELATED - Deltoid Bursitis	CS
INJECTION-RELATED - Syncope	CS

Phase 2 : Science + Policy based

- Phase 2 included further discussions within VITU-WGs and with the entire Task Force (with policy overlay).
- Out of the 21 V-AE pairs, 9 Phase 2 draft worksheets resulted (of 11 V-AE pairs) which recommended proposals for changes/updates to the VIT.
- A 10th Phase 2 worksheet was proposed to add QAI wording for “encephalitis”.

Phase 2 complete (January 2012)

IOM Causality Conclusion: Convincingly supports

Vaccine	Adverse Event	VIT Revision
Varicella	Disseminated varicella infection (widespread chickenpox rash shortly after vaccination)	Add (new)
Varicella	Disseminated varicella infection with subsequent infection resulting in pneumonia, meningitis, or hepatitis in individuals with demonstrated immunodeficiencies.	Add (new)
Varicella	Vaccine strain viral reactivation (appearance of chickenpox rash months to years after vaccination)	Add (new)
Varicella	Vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis (inflammations of the brain)	Add (new)
MMR	Measles inclusion body encephalitis	Add (under vaccine strain measles dz)
MMR	Febrile seizures (a type of seizure that occurs in association with fever and is generally regarded as benign)	No (no long-term sequelae)

IOM Causality Conclusion: Convincingly supports

Vaccine	Adverse Event	VIT Revision
MMR	Anaphylaxis (a very rare but sudden allergic reaction)	No (already there)
Varicella	Anaphylaxis	Add (new)
Influenza	Anaphylaxis	Add (new)
Hepatitis B	Anaphylaxis	No (already there)
Tetanus Toxoid	Anaphylaxis	No (already there)
Meningococcal	Anaphylaxis	Add (new)
Injection-Related Event	Deltoid bursitis (frozen shoulder, characterized by shoulder pain and loss of motion)	Add (to all injected)
Injection-Related Event	Syncope (fainting)	Add (to all injected)

IOM Causality Conclusion: Favors Acceptance

Vaccine	Adverse Event	IOM Causality Conclusion (VIT Revision)
HPV	Anaphylaxis	Favors Acceptance (Add-new)
MMR	Transient arthralgia (temporary joint pain) in women	Favors Acceptance [a] (No – no long term sequelae)
MMR	Transient arthralgia in children	Favors Acceptance (No – no long term sequelae)
Influenza	Oculorespiratory syndrome (a mild and temporary syndrome characterized by conjuctivitis, facial swelling, and upper respiratory symptoms)	Favors Acceptance [b] (No – particular vaccine not manufactured)

[a] The committee attributes causation to the rubella component of the vaccine

[b] The committee attributes causation to 2 particular vaccines used in three particular years in Canada

IOM Causality Conclusion: Favors Rejection

Vaccine	Adverse Event	IOM Causality Conclusion (VIT Revision)
MMR	Autism	Favors Rejection (No – not currently listed)
Influenza	Inactivated influenza vaccine and Bell's palsy (weakness or paralysis of the facial nerve)	Favors Rejection (No – not currently listed)
Influenza	Inactivated influenza vaccine and asthma exacerbation or reactive airway disease episodes in children and adults	Favors Rejection (No – not currently listed)
MMR	Type 1 diabetes	Favors Rejection (No – not currently listed)
DT, TT, or aP containing	Type 1 diabetes	Favors Rejection(No – not currently listed)

IOM Causality Conclusion: Inadequate to accept or reject

Vaccine	Adverse Event	VIT Revision
Influenza	Asthma exacerbation	No – no long term sequelae
Influenza	Febrile seizures	No – no long term sequelae
Influenza	Guillian-Barre Syndrome (GBS)	Deferred [a]
Hepatitis A	Anaphylaxis	No – evidence not available
DT, TT, or aP containing	Encephalopathy/encephalitis	Yes – already listed on Table but QAI will be updated
Injection-Related	Complex Regional Pain Syndrome	No – not enough evidence yet

[a] *Waiting for peer-reviewed H1N1 active surveillance publications as trivalent flu vaccines containing the H1N1 strain are being submitted to the VICP.*

Acknowledgements: VITU Task Force Membership

CDC lead: Tom Shimabukuro
HRSA lead: Rosemary Johann-Liang
Administrative Support: Scott Beach

Vaccine/Topic	Primary ISO reviewer	Secondary ISO reviewer	OGC reviewer	Primary HRSA reviewer WG-LEADS	Project Officer Review
Varicella	Mike McNeil, Zanie Leroy	Jonathan Duffy, Shahed Iqbal	Elizabeth Saindon	Catherine Shaer	Rosemary Johann-Liang
Trivalent influenza	Tom Shimabukuro	Karen Broder, Penina Haber, Jorge Arana	Elizabeth Saindon	Sarah Atanasoff	Rosemary Johann-Liang
Hepatitis B	Mike McNeil	Pedro Moro	Emily Levine	Marco Melo	Rosemary Johann-Liang
Human papillomavirus	Theresa Harrington, Julianne Gee	Claudia Vellozzi	Anna Jacobs	Barbara Shoback	Rosemary Johann-Liang
Hepatitis A	Maria Cano	Mike McNeil	Anna Jacobs/ Andrea Davey	Marco Melo	Rosemary Johann-Liang
Meningococcal	Jonathan Duffy	Maria Cano	Elizabeth Saindon	Tom Ryan	Rosemary Johann-Liang
MMR	Jane Gidudu	Maria Cano, Zanie Leroy	Anna Jacobs	Mary Rubin	Rosemary Johann-Liang
DTaP/other tetanus-containing	Pedro Moro	Jorge Arana	Emily Levine	Stacy Stryer	Rosemary Johann-Liang
Injection-related	Beth Hibbs	Elaine Miller, Tom Shimabukuro	Emily Levine	Tom Ryan	Rosemary Johann-Liang

Project Timeline in Brief (subject to clearance time)

When	Tasks Involved
9/7/11	Organizing meeting of VIT Update-Task Force
End of 9/2011	Kick-off Meeting for the VITU-TF: Each of the 8 vaccine sections + Injection-related section of the IOM report will be reviewed by 9 Working Groups composed of reviewers from DVIC/HRSA, ISO/CDC and OGC
10/2011 to 2/2012	Primary internal review of the IOM Report by the 9 WGs to generate initial draft proposed changes to the VIT (and Aids to Interpretation)
2/2012	Immunization Safety Task Force Consultation
3/2012	ACCV Consultation
9-12/2012	Notice to Public Rule Making (NPRM) publication with public hearing 12/12 ???
3/13 to 9/2013	End of 6-month public comment period followed by addressing comments and clearance of Final Rule (9/13: second opportunity if needed to seek ACCV consultation)
12/2013	Publication of Final Rule (Federal Register)/Briefing

ACCV Recommendation

Choices

1. ACCV concurs with the proposed change(s) to the VIT (and Aids to Interpretation) and would like to move forward (with or without comments)

2. ACCV does not concur with the proposed change(s) to the VIT (and Aids to Interpretation) and would not like to move forward

3. ACCV would like to defer a recommendation on the proposed change(s) to the VIT (and Aids to Interpretation) pending further review at this meeting, or the next ACCV meeting June 14-15, 2012.

PDMJ

Primary Doctor
Medical Journal

Spring 2021

Data that disprove the COVID-19 pandemic

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https://pdmj.org/papers/is_there_a_pandemic/

Colleen Huber,[i] Boris Borovoy,[ii]

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Abstract

A pandemic that calls the attention of the public, and action by the medical field, is one that raises the total death rate above that of a typical year or season. The COVID-19 era that began in early 2020 has received continuous and rapt attention in the United States for deaths that have occurred. Has COVID-19 resulted in more deaths (known as "excess deaths") than would have happened in a typical year? An obstacle to answering that question is that COVID-19 testing is flawed and imprecise, for reasons discussed herein, and it is difficult to distinguish COVID-19 from other respiratory illnesses, due to symptoms and signs that are mostly indistinguishable from the common cold, flu or pneumonia. It is possible that deaths of multiple causes have been ascribed to COVID-19, especially due to new peculiarities in mortality reporting during 2020 discussed herein. Therefore, year-over-year comparison of deaths from all causes is likely the best analysis of available evidence of whether the United States is now confronted by a deadly pandemic. The CDC mortality numbers are as yet unaudited by independent parties. Therefore, we compare numbers of obituaries in 2020 and 2019, which are verifiable reports of deaths of specific, identified individuals. We also examine the earnings statements of the largest medical suppliers in the US, to see if their sales of medical oxygen and other medical equipment prove a pandemic. These data all indicate that there has been no pandemic in the US in 2020.

[i] Colleen Huber, NMD is a Naturopathic Medical Doctor and Naturopathic Oncologist (FNORI), writing on topics of masks, COVID-19, cancer and nutrition.
[ii] Boris A Borovoy, MPH has a Master in Public Health from Moscow Medical Academy.

Background

A pandemic is the prevalent spread of a disease over an entire country or worldwide, and there is often increased mortality for its duration compared to more typical years. Early rises in death rate are a warning of an especially dangerous pandemic. In 2020, it has been widely assumed that COVID-19 is an unusually deadly pandemic.

Understanding the COVID-19 phenomenon has been obstructed by several factors.

COVID-19 is assumed to be caused by a coronavirus that is said to be novel, "SARS-Cov-2." However, SARS is likely a misnomer, because it is an abbreviation of Severe Acute Respiratory Syndrome. It is not at all clear that a majority or even a significant minority of COVID-19 patients have had acute respiratory distress with this illness. Other factors, such as use of over-pressurized ventilators, have led to acute respiratory distress among COVID-19 patients.

The most confusing aspect of COVID-19 is reliance on a manufacturing technique, now nearly universally re-purposed as a test for the presence of the SARS-Cov-2 virus, although there are many problems with this "test." We list these problems below:

1. The very questionable applicability of the manufacturing technique, the reverse-transcriptase / polymerase chain reaction technique for propagating RNA, now used throughout the world as a test for presence of the particular infectious agent in question, or of other coronaviruses, virions and virus particles that may resemble or share common nucleic acid sequences with the SARS-Cov-2 infectious agent, without distinction among those; and
2. The 80% and higher false positive rate of this "test" in the diagnosis of COVID-19, partially due to cross-immunity to fragments of other coronaviruses, inevitably present in the human body,[1] [2] followed by political pressure to recant these findings; and
3. The arbitrary number of iterations of this "test" (cycle thresholds) that must be selected to produce a positive "result"; and
4. Instructions given to physicians by the CDC to code cases as COVID-19 deaths including presumptively, even though multiple severe co-morbidities are typical among individuals whose deaths were called COVID-19; [3] and
5. Controversy regarding higher Medicare and private insurance reimbursement for COVID-19 patients than for flu patients,[4] [5] which may have skewed reported cause of death on death certificates; and
6. Generous financial rewards to hospitals by the US CARES Act for the number of COVID-19 patients they treat; and
7. The possibility that there may be political influences in altering the true number of deaths from COVID-19.

Two of these problems in particular merit greater attention.

COVID-19 has been very heavily marketed as a pandemic to the US public, with two important aspects that led to false reporting of US mortality data for COVID-19.

The incentive for mis-stated US mortality data is the financial influence created by the US CARES Act, which budgeted $175 billion dollars for distribution to hospitals for treatment of COVID-19 patients, with many hospitals receiving millions of dollars in such aid.[6] Specific financial incentives that favored COVID-19 diagnosis over other similar diagnoses such as flu, pneumonia and bronchitis especially, included a Medicare incentive of only $5,000 per patient for pneumonia, but $13,000 per patient for the pathologically indistinguishable COVID-19 pneumonia. [7] [8] Further, the CARES Act incentive of $39,000 to treat such a patient with a ventilator resulted in financially lucrative outcomes for hospitals, but medically lethal outcomes for patients.[9]

The core of public confusion and fear of COVID-19 stems from the testing itself. Reverse-transcriptase, polymerase chain reaction (RT-PCR) is a manufacturing technique for producing more RNA nucleic acid sequences. It was not intended by its inventor, the late Kary Mullis, PhD, as a test for an infectious disease. He warned against its use in such an application. He especially warned that it could be misused if the cycles, or iterations, of this procedure were processed too many times on a particular specimen. Regarding the use of RT-PCR to attempt to detect infectious disease, he said, at 35 or 40 cycles, "you can find almost anything in anybody."[10] The CDC acknowledges that 33 cycles or more are unlikely to detect active virus.[11] The number of cycles used in "COVID-19 testing" in the US have been above 37, and often well into the 40's for all of 2020.[12] [13] Laboratories in the US do not disclose the cycle thresholds that they use in running RT-PCR SARS-CoV-2 tests, except in Florida where the disclosure is mandatory.[14] No standardization for cycle threshold values exists across different tests and different laboratories.[15]

Infectivity was found to be significantly reduced from positive tests when cycles were greater than 24, and that for every 1-unit increase in cycle threshold, the odds ratio of infectivity decreased by 32%.[16] Researchers concluded that PCR sensitivity is excellent (can find viral particles very easily), but that its specificity for detecting replicative (active) virus is poor,[17] as Dr. Mullis had warned. Nevertheless, RT-PCR has become "the COVID-19 test" used ubiquitously throughout the US and many other countries.

The magnitude of deception resulting from this misuse, overuse, over-cycling and over-advertising of PCR as a COVID-19 testing technique, along with frequent exhortations by politicians to "get tested," can hardly be overstated. This is the core of the problem of the public falsely believing that there is a pandemic, and that its name is COVID-19.

Therefore, in order to attain the truest picture of the impact of the COVID-19 on public health, it would be helpful to look at deaths from all causes, to see if there has been a significant change.

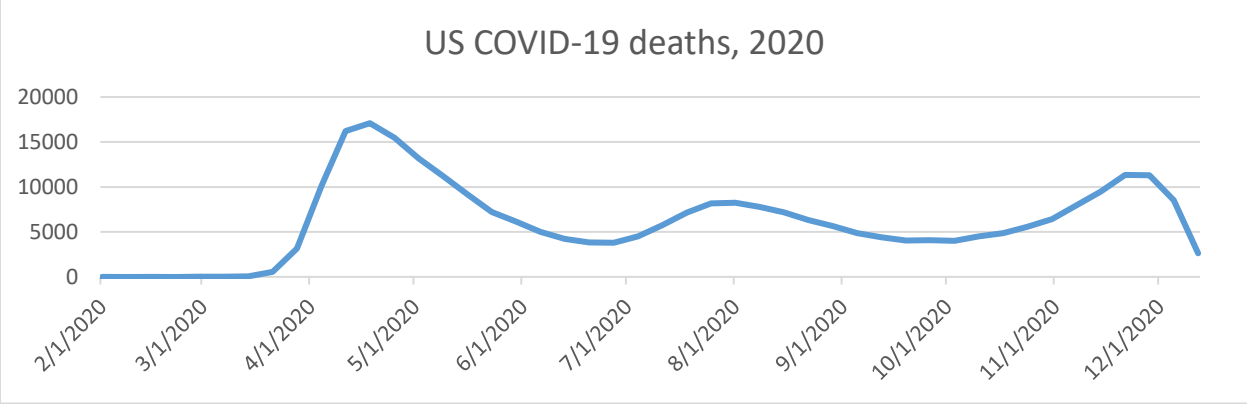
https://pdmj.org/papers/is_there_a_pandemic/

Deaths attributed to COVID-19 are at the oldest ages; yet age distribution of all-cause mortality did not significantly change during weeks of peak reported COVID-19 deaths

Researcher Genevieve Briand PhD hypothesized that the over-counting of COVID-19 death numbers may be due to society's heavy focus on that topic, which would eclipse awareness or even reporting of more typical causes of death.[18]

Dr. Briand found that the proportion of total deaths in US by age group did not change from before COVID-19 to after its peak incidence in the US. The CDC has shown throughout 2020 that peak incidence of COVID-19 deaths occurred the weeks ending April 11 and April 18, 2020,[19] as shown in this graph:

Graph 1

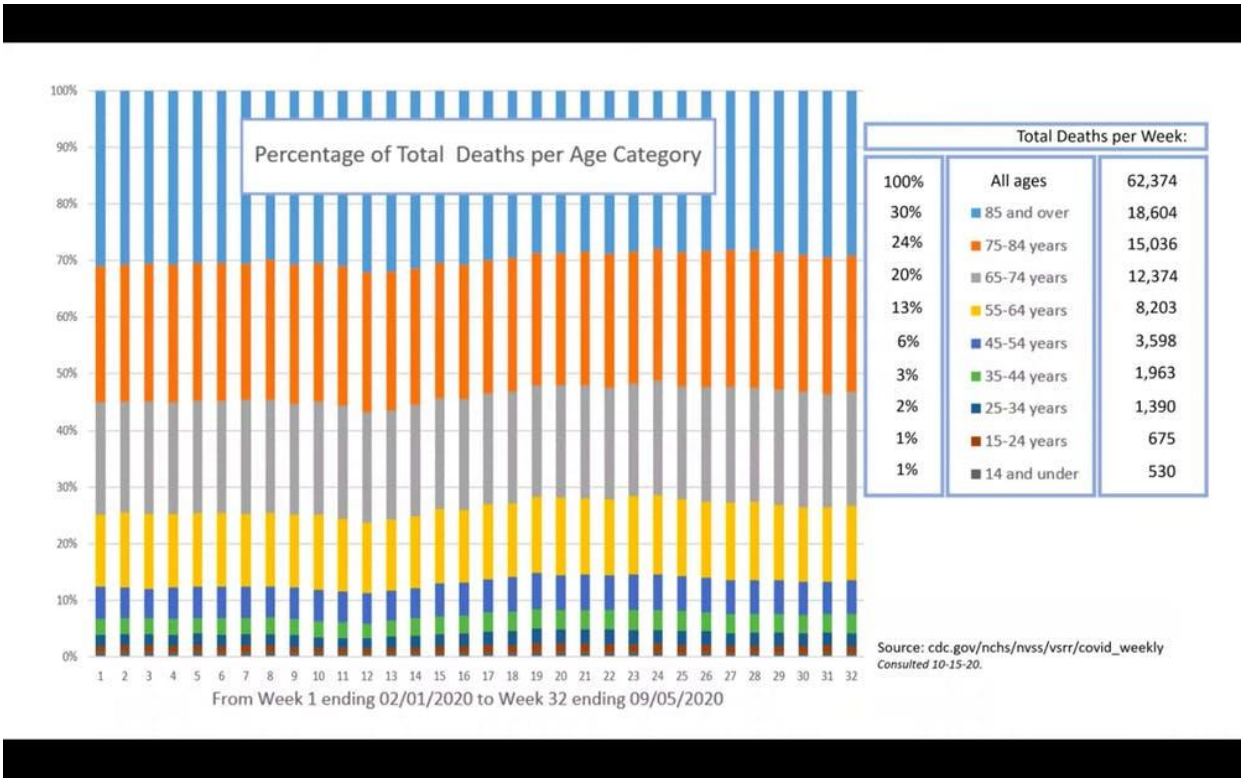


Briand's research showed that for all weeks of 2020 to date, a consistent proportion, among different age groups, of deaths from all causes occurred. Her research was quickly removed from the internet almost as soon as it was posted. The publisher, then censor, was Johns Hopkins University, with known financial ties to World Economic Forum and Bill and Melinda Gates Foundation, each of which has taken an active role in promoting COVID-19 as the catalyst that justifies a New World Order.[20] Several concerns regarding over-reporting of COVID-19 data are enumerated above.

Here is the clearest available photo of Dr. Briand's graph of the age distribution of total deaths from February 1, 2020, which is before COVID-19 affected the US population, before there was even one death from it, through early September 2020.

https://pdmj.org/papers/is_there_a_pandemic/

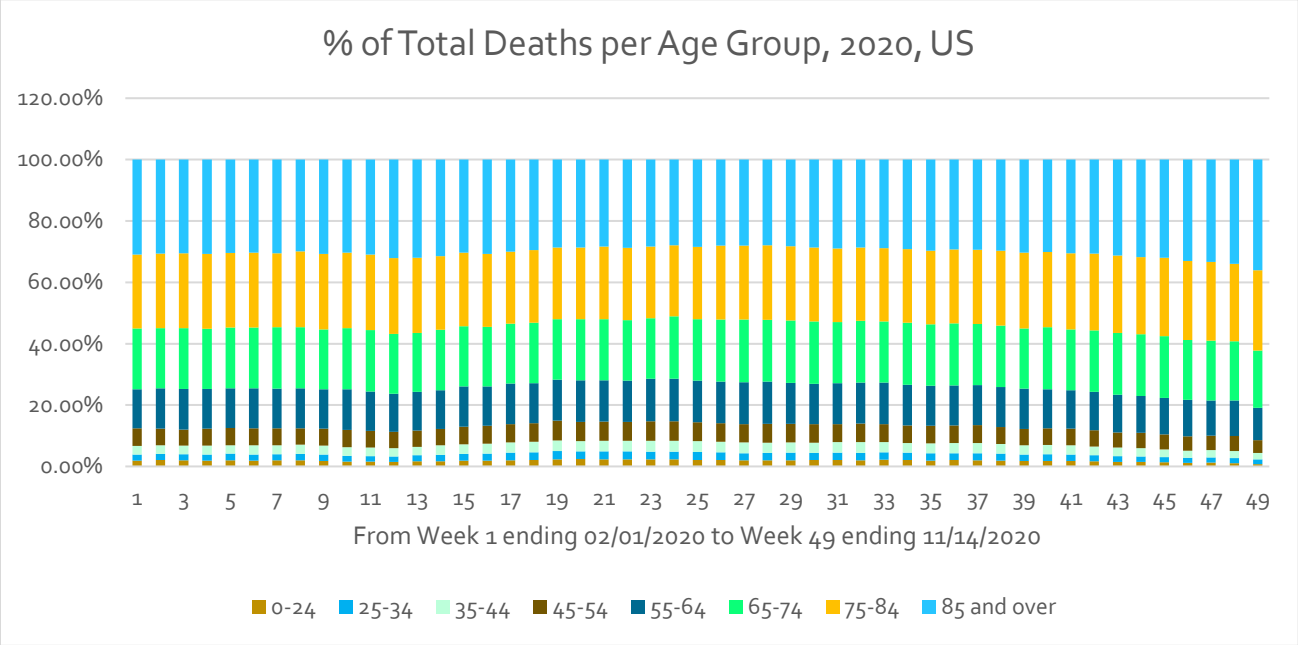
Graph by Genevieve Briand



https://pdmj.org/papers/is_there_a_pandemic/

Our updated graph, derived from CDC data through 01/02/2021 [21] of the same analysis is as follows:

Graph 2

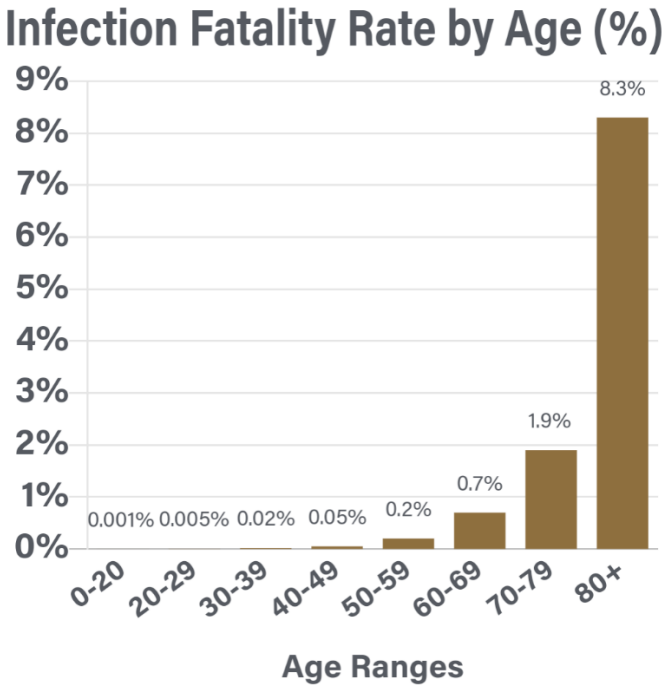


What is especially interesting about the age distribution of total deaths is that there is no extreme change at any time in 2020 of the proportion of total deaths for any age group, except for the last seven weeks, but those weeks do not correspond to COVID-19 peak mortality reporting, which was in April 2020. The CDC showed the weeks ending April 11 and April 18, 2020 (weeks 11 and 12 of the above graph) as the weeks with the highest COVID-19 deaths, yet there is barely perceptible difference in age distribution of deaths, even during those weeks. If there were a pandemic that affected all age groups equally, such a consistency over the year would not be surprising.

However, COVID-19 is a peculiar phenomenon in that the average age of death for COVID-19 is beyond the average age of total deaths. Unfortunately, regarding COVID-19, much of the important data still remains hidden. The BBC reports average age of death in Scotland is 79.1, but the average age of COVID-19 death in Scotland is 81.5.[22] The mean age of COVID-19 death in France is 79 years.[23] If there were a large number of deaths from COVID-19, with average age of death of 79 to 81, there would have been wide swings in age distribution toward the higher age groups during peak time periods of deaths that were attributed to COVID-19. In comparison with the first four weeks studied (February 2020), when there were no COVID-19 deaths, there would have been a rise in the proportion of those in the highest age categories of all deaths. However, that change did not happen. As Briand concluded, COVID-19 had no effect on the percentage of deaths of older people as a portion of the whole population.

https://pdmj.org/papers/is_there_a_pandemic/

The graph below, from Science,[24] shows the Infection Fatality Rate of COVID-19. We see that the deaths are skewed strongly toward the upper ages.



Source: Science 10 Jul 2020;, Vol. 369, Issue 6500, pp. 208-211 DOI: 10.1126/science.abc3517

The average life expectancy in the US is 78.7 to 78.9 years. [25] [26] If the average age of death from COVID-19 is above the average US life expectancy, then COVID-19 cannot be a major independent cause of death, as in cutting short the lives of people who were expected to live longer. This of course varies with individuals, but cannot vary with respect to the population as a whole.

Even from unaudited CDC data so far, it appears that COVID-19 has not made appreciable impact on the overall US death rate. From 2017 through 2020 the rate of deaths in the US population has stayed at 0.9%, keeping pace with population growth, as the following table shows. [27]

https://pdmj.org/papers/is_there_a_pandemic/

DEATHS IN US BY YEAR

Year	Deaths	Population	Deaths per 100,000	Rate
2010	2,468,435	309,346,863	798	0.8%
2011	2,515,458	311,718,847	807	0.8%
2012	2,543,279	314,102,623	810	0.8%
2013	2,596,993	316,427,395	821	0.8%
2014	2,626,418	318,907,401	824	0.8%
2015	2,712,630	321,418,820	844	0.8%
2016	2,744,248	323,071,342	849	0.8%
2017	2,813,503	325,147,121	865	0.9%
2018	2,839,205	327,167,439	868	0.9%
2019	2,855,000	328,239,523	870	0.9%
2020	2,902,664	330,767,888	878	0.9%

CDC - Census (as of 12/30/2020)
https://www.cdc.gov/nchs/nvss/vsrr/provisional-tables.htm
https://www.cdc.gov/nchs/nvss/vsrr/covid19/index.htm

(Numbers reflect all deaths, including Covid-19)

Obituary data

To understand the discrepancy between the announcement of a pandemic that affects almost entirely the elderly, yet does not change the deceased elderly as a proportion of the total deceased, we must look beyond this particular set of data.

The CDC has presented on faith their enumerated death counts. One might ask, but where is the evidence underlying these numbers? Of the largest obituary reporting services in the US, the largest of these with the most transparent data seems to be United States Obituary Notices (USObit.com.) This obituary reporting service reports the deaths of specific, verifiable deceased individuals. The total numbers of deceased reported by USOBit.com are approximately 20% to 25% of total deaths in the US as reported by the CDC. The data shown on their site for 2019 and 2020 is summarized as follows.

Table 1

Usobit.com US obituary notices	Pages of obituaries	x 12 per page	Total deaths per month	Rank				
Jan-20	4772	12	57264	1	Jan-19	7167	12	86004
Feb-20	4021	12	48252	3	Feb-19	5657	12	67884
Mar-20	3436	12	41232	10	Mar-19	5293	12	63516
Apr-20	3850	12	46200	6	Apr-19	4632	12	55584
May-20	3294	12	39528	12	May-19	3478	12	41736
Jun-20	4182	12	50184	2	Jun-19	4041	12	48492
Jul-20	3952	12	47424	4	Jul-19	4066	12	48792
Aug-20	3796	12	45552	7	Aug-19	3920	12	47040
Sep-20	3444	12	41328	9	Sep-19	4266	12	51192
Oct-20	3657	12	43884	8	Oct-19	4289	12	51468
Nov-20	3386	12	40632	11	Nov-19	4179	12	50148
Dec-20	3885	12	46620	5	Dec-19	4693	12	56316
Total US deaths accounted for by obituaries - 2020			**548100**		**Total US deaths accounted for by obituaries - 2019**			**668172**

Obituaries of real, identifiable deceased individuals declined by almost 18% from 2019 to 2020. If these obituaries are representative of deaths in the US as a whole, then it is impossible for there to be a pandemic in the United States in 2020. These deaths are at least verifiable, unlike the unaudited, unverified numbers that the CDC presents. It is also interesting that the month with the largest number of COVID-19 deaths according to the CDC, April 2020, ranks 6th out of the 12 months of 2020 regarding total obituaries. Other large obituary services did not respond to requests for information or refused to share information on total numbers of obituaries in 2019 and in 2020.

Wall Street vs the pandemic story

There are other data that suggest that there is no pandemic, at least not involving a pathogen that causes acute respiratory distress.

We looked at companies that produce and distribute medical oxygen. The following graph shows total sales over the largest of those companies actually declined from 2019 to 2020.

Table 2

Company name	NYSE symbol	SALES $ Millions	2017	2018	2019	2020	Half-year revenue 2019 Q1Q2	2019 Q3Q4	2020 Q1Q2
MED O2 PRODUCERS									
Air Products	APD		8188	8930	8919	8857			
Air Liquide	AIQUY						12360	12297	11540
Linde	LIN		11400	14800	28200	27000			
Total sales $M			19588	23730	37119	35857			
Change in medical O2 sales in 2020 from 2019						**-3.40%**			**-6.16%**
O2 CONCENTRATOR PRODUCERS									
Invacare	IVC		966.5	972.3	928	842.2			
Inogen	INGN		249.4	358.1	361.9	303.7			
Medtronic	MDT			30000	30600	28900			
Philips	PHG		20100	21400	21800	23700			
ResMed	RMD			2300	2600	3000			
Vapotherm	VAPO		35.6	42.4	48.1	117.1			
Total sales $M				**55072.8**	**56338**	**56863**			
Change in O2 concentrator over previous year					**2.30%**	**0.93%**			

At the beginning of 2020, COVID-19 had no perceptible impact on any aspect of life or business in the US. By the end of 2020, almost every facet of American life had been shaken by the phenomenon of the response to SARS-CoV-2. That is, every aspect *except* the public's need for medical oxygen. For the alleged "Severe Acute Respiratory Syndrome" for which SARS-CoV-2 was named, US citizens have actually consumed less supplemental medical oxygen in 2020 than in 2019, despite our growing population, thus disproving a 2020 pandemic involving a respiratory pathogenic virus, i.e. the now legendary SARS-CoV-2 and COVID-19.[28]

In a related market, oxygen concentrators have been recently innovated to include small, portable backpack units for individuals who are ambulatory with long-term chronic conditions requiring supplemental oxygen, which is thought to account for much of the increase in sales in 2019. This welcome innovation greatly increased mobility and convenience for those dependent on supplemental oxygen. But even those sales did not increase as much in 2020 as they had in 2019, and are mostly irrelevant to a virus thought to be as acutely sickening as SARS-CoV-2. Rather, small travel-size backpacks of oxygen concentrators are more suited to ambulatory patients with chronic COPD, pulmonary fibrosis, and other non-emergent lung diseases.

Then we looked at other medical products.

The five largest medical supply companies in the US are: McKesson, Amerisource Bergen, Henry Schein, Cardinal Health and Medline Industries.[29] Their sales for 2019 and 2020, from their corporate earnings reports[30] are compared below, as well as their change in growth over that time.

Table 3

5 largest medical suppliers		**SALES in $ Millions**					
		2019	2020		**Growth rate**		
					1 Yr	3 Yr	5 Yr
McKesson		214000	231000		5.50%	5.20%	5.20%
Amerisource Bergen		179500	189900		5.70%	7.40%	6.90%
Henry Schein		10000	9800		-1.70%	-4.80%	-0.80%
Cardinal Health		145500	152900		4.70%	5.60%	8.30%
Medline Industries	not on NYSE						
Total sales		**549000**	**583600**	**Total growth**	**14.20%**	**13.40%**	**19.60%**

Although these five companies' sales increased in 2020 over 2019, the growth rate for one year has slowed from the 5-year aggregate overall growth rate for these companies. This is even though the US population has steadily increased through those years.

Conclusion

On examination of diverse data, from CDC mortality data, to obituaries, to Wall Street earnings reports, there are enough indicators that a pandemic involving a Severe Acute Respiratory Syndrome (SARS) virus could not have taken place, at least not in the United States in 2020.

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https://pdmj.org/papers/is_there_a_pandemic/

Air Products and Chemicals Inc **APD**:NYSE
Chemicals

Trade
Margin Requirements

Last Price	Today's Change	Bid/Size	Ask/Size	Today's Volume
$286.91	+0.66 (0.23%)	$280.09/1	$292.38/2	1,908,635 Above Avg.

As of close Friday, 01/15/2021

Schwab Equity Rating® Data as of 01/08/2021*

First Quarter Earnings Announcement Expected

Summary | News | Charts | Ratings | **Earnings** | Statements | Peers | Ratios | Dividends | Reports | Options | Preferreds

Earnings | Estimates | Trends

Growth Analysis (Fiscal Year Ending September 30, 2020)

Vickers Insider Prophets Report | Reuters Investment Profile

Quarterly | Annual

Show Price Chart | Hide Price Chart

Earnings Per Share

Non-GAAP | **GAAP**

Positive/Negative Restatement | Recent Restatement

+14.8% Annualized 5 Year growth rate

Growth Rates (GAAP)

1 Yr	3 Yr	5 Yr
+8.5%	+18.3%	+14.8%

1 Yr Growth rate is trailing twelve months (TTM) compared to the previous twelve months. 3 and 5 Yr are compound annual growth rates (CAGR). Place your mouse over the bar to view GAAP and Non-GAAP results.

Revenue (Sales) (Numbers shown in Billions)

Current Quarter vs. Prior Year:

For the first quarter 2021, analysts estimate APD will generate revenues of $2.3B, an increase of 4.01% over the prior year first quarter results.

+2.5% Annualized 5 Year growth rate

Growth Rates

1 Yr	3 Yr	5 Yr
-0.7%	+2.7%	+2.5%

https://pdmj.org/papers/is_there_a_pandemic/

L'Air Liquide Societe Anonyme pour l'Etude et l'Exploitation des Procedes
George **AIQUY** OTC Pink - Current Information OTC ADR
Chemicals

Last Price	Today's Change	ADR Ratio	Bid/Size	Ask/Size	Today's Volume
$32.89	-0.18 (-0.54%)	5:1	$32.78/1,000	$33.64/100	90,191 Below Avg.

As of close Thursday, 12/31/2020

Schwab Equity Rating International® within France, data as of 12/31/2020*

The Economist Intelligence Unit© Country Risk Level as of 12/02/2020

You may be charged fees by the Bank that custodies this ADR. Read More about ADR pass-through fees.
This stock may be available for trading through a Schwab Global Account. Learn More

Trade

Compare Exchanges

Other Quotes For This Company

AIQUY	OTC Pink - Curr...	$USD 32.89
AI:XPAR	Euronext Paris	€EUR 134.25
AIQUF	OTC Pink - Curr...	$USD 167.06

Quotes FAQ Margin Requirements

Summary | News | Charts | Ratings | Earnings | **Statements** | Peers | Ratios | Dividends | Reports | Options | Preferreds

Income Statement | Balance Sheet | Cash Flow Statement

Income Statement (Fiscal Year Ending in December) *Converted Values in $USD*

Quarterly | Annual

Detail View | Summary View

Values are in Millions, except for per share data. Quarters are Fiscal Quarters. ( ) = Negative	Quarterly Trend	Q2 2020 6/30/2020 6 Months	Q4 2019 12/31/2019 6 Months	Q2 2019 6/30/2019 6 Months	Q4 2018 12/31/2018 6 Months	Q2 2018 6/30/2018 6 Months
Revenue & Gross Profit						
Total Revenue		***11,540***	***12,297***	***12,360***	***12,444***	***11,875***
Operating Expenses						
Cost of Revenue, Total		*4,079*	*4,399*	*4,774*	*4,964*	*4,614*
Labor & Related Expense		*2,452*	*2,497*	*2,464*	*2,414*	*2,386*
Sell/Gen/Admin Expenses, Total		*2,452*	*2,497*	*2,464*	*2,414*	*2,386*
Depreciation		*1,120*	*1,105*	*1,106*	*919*	*926*
Amortization of Intangibles		*98*	*99*	*94*	*99*	*101*

https://pdmj.org/papers/is_there_a_pandemic/

Linde PLC **LIN**:NYSE
Chemicals

Trade
Margin Requirements

Last Price	Today's Change	Bid/Size	Ask/Size	Today's Volume
$258.09	-5.60 (-2.12%)	$258.00/1	$265.88/1	1,955,553 Average

As of close Friday, 01/15/2021

Schwab Equity Rating® Data as of 01/08/2021*

Fourth Quarter Earnings Announcement Expected

Summary | News | Charts | Ratings | **Earnings** | Statements | Peers | Ratios | Dividends | Reports | Options | Preferreds

Earnings | Estimates | Trends

Growth Analysis (Fiscal Year Ending December 31, 2019)

Reuters Investment Profile

Quarterly | Annual

Show Price Chart | Hide Price Chart

Earnings Per Share

Non-GAAP | **GAAP**

Positive/Negative Restatement Recent Restatement

-6.9% Annualized 5 Year growth rate

Growth Rates (GAAP)

1 Yr	3 Yr	5 Yr
-57.9%	-8.4%	-6.9%

1 Yr Growth rate is trailing twelve months (TTM) compared to the previous twelve months. 3 and 5 Yr are compound annual growth rates (CAGR). Place your mouse over the bar to view GAAP and Non-GAAP results.

Revenue (Sales) (Numbers shown in Billions)

Current Quarter vs. Prior Year:

For the fourth quarter 2020, analysts estimate LIN will generate revenues of $7.0B, a decrease of 0.47% over the prior year fourth quarter results.

+18.1% Annualized 5 Year growth rate

Growth Rates

1 Yr	3 Yr	5 Yr
+0.4%	+38.9%	+18.1%

The truth behind the vaccine cover-up

Russell L. Blaylock, MD
Website: www.russellblaylockmd.com

Abstract

On June 7-8, 2000 a secret conference was held at the Simpsonwood Conference Center in Norcross, Georgia to discuss a study examining the link between increasing doses of Thimerosal and neurodevelopmental disorders. The study was done using the Vaccine Safety Datalink (VSD) database, an official governmental data bank collecting patient vaccination information on the children from the health maintenance organizations (HMOs) being paid to participate. Attending were 51 scientists, representatives of pharmaceutical vaccine manufacturing companies and a representative of the World Health Organization; the public and the media were unlawfully excluded. The conclusions of this meeting were quite startling, since it confirmed a dose-response link between Thimerosal and neurodevelopmental disorders that held up to rigorous statistical analyses.

In their discussion, they make plain why the meeting was held in secret: the conclusions would have destroyed the public's confidence in the vaccine program, and more importantly, their faith in vaccine authorities. When the results of this study were published three years later in the journal *Pediatrics*, the "problem" had been fixed, in that by adding another set of data from a third HMO, reorganizing the criteria for inclusion and restructuring the patient groupings, a less than statistically significant link was demonstrated. In my analysis I discuss the more outrageous statements made during the meeting and how accepted experts in the field of mercury neurotoxicity were excluded from the meeting.

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Keywords: Thimerosal-containing vaccines, Vaccine Safety Database (VSD), Thimerosal exposure, Thimerosal neurotoxicity, aluminum neurotoxicity

I was asked to write a paper on some of the newer mechanisms of vaccine damage to the nervous system, but in the interim I came across an incredible document that should blow the lid off the cover-up being engineered by the pharmaceutical companies in conjunction with powerful governmental agencies.

It all started when a friend of mine sent me a copy of a letter from Congressman David Weldon, M.D. to the director of the CDC, Dr Julie L. Gerberding, in which Congressman Weldon alludes to a study by a Doctor Thomas Verstraeten, then representing the CDC, on the connection between infant exposure to Thimerosal-containing vaccines and neurodevelopmental injury. In this shocking letter, Congressman Weldon refers to Dr. Verstraeten's study, which looked at the data from the Vaccine Safety Datalink and found a statistically significant correlation between Thimerosal exposure via vaccines and several neurodevelopmental disorders including tics, speech and language delays, and possibly ADD.

Congressman Weldon questions the CDC director as to why, following this meeting, Dr. Verstraeten published his results almost four years later in the journal *Pediatrics* to show just the opposite, that is, that except for tics, there was no statistically significant correlation to any neurodevelopmental problems related to Thimerosal exposure in infants. In this letter, Congressman Weldon refers to a report of the minutes of this meeting held in 2000, which exposes some incredible statements by the "experts" making up this study group. The group's purpose was to evaluate and discuss Dr. Verstraeten's interim results and data and make recommendations that would eventually lead to possible alterations in existing vaccine policy.

I contacted Congressman Weldon's legislative assistant and he kindly sent me a complete copy of this report. Now, as usual in these cases, the government did not give up this report willingly; it required a Freedom of Information Act lawsuit to pry it loose. Having read the report twice and having carefully analyzed it, I can see why they did not want any outsiders to see it. It is a bombshell, as you shall see.

To help the reader understand the importance of this report, in this analysis I will not only describe and discuss this report, but also will frequently quote their words directly and supply the exact page number so others can see for themselves.

The official title of the meeting was the "**Scientific Review of Vaccine Safety Datalink Information.**" This conference, held on June 7-8, 2000, at Simpsonwood Retreat Center in Norcross, Georgia, assembled 51 scientists and physicians, five of whom represented vaccine manufacturers. These included Smith Kline Beecham, Merck, Wyeth, North American Vaccine and Aventis Pasteur.

During this conference, these scientists focused on the study of the Datalink material, whose main author was Dr. Thomas Verstraesten and who identified himself as working at the National Immunization Program of the CDC. It was discovered by Congressman Weldon that Dr. Verstraeten left the CDC shortly after this conference to work for the Belgian operations of the pharmaceutical maker GlaxoSmithKline—a recurring regulated agency/regulated-industry pattern that has been given the name "a revolving door". It is also interesting to note that GlaxoSmithKline was involved in several lawsuits over complications secondary to their vaccines.

To start off the meeting, Dr. Roger Bernier, Associate Director for Science in the National Immunization Program (CDC), related some pertinent history. He stated that Congressional action in 1997 required that the FDA review mercury being used in drugs and biologics (vaccines). To meet this mandate, the FDA called for all the registered manufacturers of drugs, including vaccines, to submit the mercury information about their drug products. He notes that a group of European regulators and manufacturers met on April 1999 and acknowledged the situation but made no recommendations or changes. In other words, it was all for show.

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At this point Dr. Bernier makes an incredible statement (page 12). He says, "**In the United States there was a growing recognition that cumulative exposure may exceed some of the guidelines."** By guidelines, he is referring to guidelines for mercury exposure safety levels set by several regulatory agencies. The three guidelines were set by the ATSDR (The Agency for Toxic Substances and Disease Registry), the FDA (Food and Drug Administration), and the EPA (Environmental Protection Agency). The most consistently violated safety guideline was the mercury-in-food limit set by the EPA. He further explains that he is referring to children being exposed to Thimerosal in vaccines.

Based on this realization that they were violating safety guidelines, he says that this then "**resulted in a joint statement of the Public Health Service (PHS) and the American Academy of Pediatrics (AAP) in July of last year (1999), which stated that as a long term goal, it was desirable to remove mercury from vaccines because it was a potentially preventable source of exposure."** (Page 12)

As an aside, one has to wonder, where was the Public Health Service and American Academy of Pediatrics during all the years of mercury use in vaccines and why didn't they know that, number one, they were exceeding regulatory safety levels and secondly, why weren't they aware of the extensive literature showing deleterious effects on the developing nervous system of babies? As we shall see, even these "experts" seem to be cloudy on the mercury literature.

Dr. Bernier notes that in August 1999 a public workshop was held in the Lister Auditorium in Bethesda by the National Vaccine Advisory Group and the Interagency Working Group on Vaccines to consider Thimerosal risk in vaccine use. And based on what was discussed in that conference,Merck, one manufacturer of a U.S.-licensed hepatitis B vaccine (HepB) moved to license a "no Thimerosal" formulation for young children but kept making and distributing its Thimerosal-preserved HepB formulation into the mid 2000s while GlaxoSmithKline, the other U.S.-licensed HepB maker apparently moved to license a reduced-Thimerosal formulation; apparently, neither firm moved to recall the existing Thimerosal-preserved doses. It is interesting to note that the media took very little interest in what was learned at that meeting and it may have been a secret meeting—probably because it was also a meeting that was not, as required by law, announced publicly. As we shall see, there is a reason why they struggle to keep the contents of all these meetings secret from the public.

Dr. Bernier then notes on page 13 that on October 1999 the Advisory Committee on Immunization Practices (ACIP) **"looked this situation over again and did not express a preference for any of the vaccines that were Thimerosal free."** In this discussion he further notes that the ACIP concluded that the Thimerosal-containing vaccines could be used but the "**long-term goal"** is to try to remove Thimerosal as soon as possible.

Now, we need to stop and think about what has transpired. We have an important group here, the ACIP that essentially plays a role in vaccine policy affecting tens of millions of children every year. And, we have evidence from the Thimerosal meeting in 1999 that the potential for serious injury to the infant's brain is so serious that a recommendation for removal becomes policy. In addition, they are all fully aware that tiny babies are receiving mercury doses that exceed even EPA safety limits for adults, yet all they can say is that we must "try to remove Thimerosal as soon as possible." Do they not worry about the tens of millions of babies who will continue receiving Thimerosal-containing vaccines until they can get around to stopping the use of Thimerosal?

It should also be noted that it is a misnomer to say "removal of Thimerosal" since they are not removing anything. They just plan to stop adding it to future vaccines once they use up existing stocks, which entails millions of doses. And incredibly, the government allows them to do it. Even more incredibly, the **American Academy of Pediatrics** and the **American Academy of Family Practice** similarly endorse this insane policy. In fact, they specifically state that children should continue to receive the Thimerosal-containing vaccines until new Thimerosal-free vaccines can be manufactured at the will of the manufacturers. It was disclosed that Thimerosal was in all influenza, HepB and DPT vaccines, as well as most DtaP vaccines

Had vaccine safety been their primary concern, as it should be, the most obvious solution was to recommend only single-dose vials, which require no preservative, coupled with a ban on the use of any mercury compound in the manufacture of all drugs. So, why didn't they make this or at least a "no Thimerosal" recommendation? "Oh," they exclaim, "it would add to the cost of the vaccine." Of course, we are only talking about a few dollars per vaccine at most, certainly worth the health of your child's brain and future. They could use some of the hundreds of millions of dollars they waste on vaccine promotion every year to cover the cost for the poor. Yet, that would cut into some fat-cat's profit and we can't have that.

As they begin to concentrate on the problem at hand we first begin to learn that the greatest problem with the meeting is that they know virtually nothing about what they are doing. On page 15, for example, they admit that there is very little pharmacokinetic data on ethylmercury, the form of mercury in Thimerosal. In fact, they say there is no data on excretion and the data on toxicity is sparse; yet it is recognized to cause hypersensitivity, neurological problems, and even death, and it is known to easily pass the blood-brain barrier and the placental barrier.

Therefore, what they are admitting is that we have a form of mercury that has been used in vaccines since the 1930s and no one has bothered to study the effects on biological systems, especially the brains of infants. Their defense throughout this conference is "**we just don't know the effects of ethylmercury.**" As a solution, they resort to studies on methylmercury because there are thousands of studies on this form of mercury. The major source of this form is seafood consumption.

It takes them awhile to get the two forms of mercury straight, since for several pages of the report they say methylmercury is in Thimerosal rather than ethylmercury. They can be forgiven for this. On page 16, Dr. Johnson, an immunologist and pediatrician at the University of Colorado School of Medicine and the National Jewish Center for Immunology and Respiratory Medicine, notes that he would like to see the incorporation of wide margins of safety, that is **3 to 10-fold margins of safety** to "**account for data uncertainties**." What he means is that there are so many things we do not know about this toxin

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that we had better use very wide margins of safety. For most substances the FDA uses a 100-fold margin of safety.

The reason for this, which they do not mention, is that in a society of hundreds of millions of people, there are groups of people who are much more sensitive to the toxin than others. For instance, the elderly, the chronically ill, the nutritionally deficient, small babies, premature babies, those on certain medications and those with inborn defects in detoxification, just to name a few. In fact, premature babies and low birth weight babies were excluded from the main study since (1) some had the highest mercury levels, (2) these would be hard to study, and (3) they had the most developmental problems possibly related to the mercury. In other words, including these babies might endanger their claims of safety.

It should also be noted that all participants at this conference ignored the differences in total mercury exposure among infants and small children living in different geographical areas. For example, a child's mother who had dental amalgams, who regularly eats high-methymercury-containing seafood and lives in an area with high atmospheric mercury levels will have much higher total mercury exposure than one exposed to little dietary, dental, and environmental mercury.

Also on page 16, Dr. Johnson makes an incredible statement, one that defines the problem we have in this country with the promoters of these vaccines. He states, **"As an aside, we found a cultural difference between vaccinologist and environmental health people in that many of us in the vaccine arena have never thought about uncertainty factors before. We tend to be relatively concrete in our thinking."** Then he says, **"One of the big cultural events in that meeting... was when Dr. Clarkson repetitively pointed out to us that we just didn't get it about uncertainty, and he was actually quite right."**

This is an incredible admission. First, what is a "vaccinologist"? Do you go to school to learn to be one? How many years of residency training are required to be a "vaccinologist"? Are there board exams? It's an ill-defined term used to describe people who are obsessed with vaccines, not that they actually study the effects of the vaccines, as we shall see throughout this meeting. Most important is the admission by Dr. Johnson that he and his fellow "vaccinologists" are so blinded by their obsession with forcing vaccines on society that they never even considered that there might be factors involved that could greatly affect human health, the so-called **"uncertainties"**. Further, he admits that he and his fellow "vaccinologists" like to think in concrete terms; that is, they are very narrow in their thinking and wear blinders that prevent them from seeing the numerous problems occurring with large numbers of vaccinations in infants and children. Their goal in life is to vaccinate as many people as possible with an ever-growing number of vaccines.

On page 17 his **"concrete thinking"** once again takes over. He refers to the Bethesda meeting on Thimerosal safety issues and says**, "there was no evidence of a problem, only a theoretical concern that young infants' developing brains were being exposed to an organomercurial."** Of course, as I shall point out later, it is a lot more than a "theoretical concern". He then continues by saying, **"We agree that while there was no evidence of a problem, the increasing number of vaccine injections given to infants, was increasing the theoretical mercury exposure risk."**

It's hard to conceive of a true scientist not seeing the incredible irony of these statements. The medical literature abounds with studies on the deleterious effects of mercury on numerous enzymes, mitochondrial energy production, synaptic function, dendritic function, neurotubule dissolution and excitotoxicity—yet he sees only a "theoretical risk" associated with an ever increasing addition of Thimerosal-containing vaccines. It is also important to note that these geniuses never even saw a problem in the first place, it was pressure from outside scientists, parents of affected children, and groups representing them that pointed out the problem. They were, in essence, reacting to pressure from outside the "vaccinologist club" and, therefore, had not discovered internally that a problem even "might" exist.

In fact, if these outside groups had not become involved, these "vaccinologists" would have continued to add more and more mercury-containing vaccines to the list of required vaccines. Only when the problem became so obvious, that is of epidemic proportion and the legal profession became involved, would they have even noticed there was a problem. This is a recurring theme in the government's regulatory agencies, as witnessed with fluoride, aspartame, MSG, dioxin and pesticides issues.

It is also interesting that Dr. Johnson did admit that the greatest risk was among low birth weight infants and premature infants. Now why would that be if there existed such a large margin of safety with mercury used in vaccines? Could just a few pounds of body weight make such a dramatic difference? In fact, it does, but it also means that normal birth weight children, especially those near the low range of normal birth weight, are also in greater danger. It also would mean that children receiving doses of mercury higher than the 75 ug in this study would be at high risk as well because their dose, based on body weight, would be comparable to that of the low birth weight child receiving the lower dose. This is never even considered by these "vaccinologist" experts who decide policy for your children.

Now this next statement should shock everyone, but especially the poor who might believe that these "vaccinologist" experts have their best interest in mind. Dr. Johnson says on page 17, **"We agree that it would be desirable to remove mercury from U.S. licensed vaccines, but we did not agree that this was a universal recommendation that we would make because of the issue concerning preservatives for delivering vaccines to other countries, particularly developing countries, in the absence of hard data that implied that there was in fact a problem."**

So, here you have it. The data is convincing enough that the American Academy of Pediatrics and the American Academy of Family Practice, as well as the regulatory agencies and the CDC, all recommend its removal as quickly as possible because of concerns of adverse effects of mercury on brain development, but not for the children in the developing countries. I thought the whole idea of child health programs in the United States directed toward the developing world was to give poor children a better chance in an increasingly competitive world. This policy being advocated would increase the neurodevelopmental problems seen in poor children of developing countries

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and of this country, impairing their ability to learn and develop competitive minds. Remember, there was a representative of the World Health Organization (WHO), Dr. John Clements, serving on this panel of "experts" who apparently never challenged this statement made by Dr. Johnson.

It also needs to be appreciated that children in developing countries are at a much greater risk of complications from vaccinations and from mercury toxicity than children in developed countries. This is because of poor nutrition, concomitant parasitic and bacterial infections, and a high incidence of low birth weight in these children. We are now witnessing a disaster in African countries caused by the use of older live virus polio vaccines that has now produced an epidemic of vaccine related polio, that is, polio caused by the vaccine itself. In, fact, in some African countries, polio was not seen until the vaccine was introduced.

The WHO and the "vaccinologist experts" from this country now justify a continued polio vaccination program with this dangerous vaccine on the basis that now that they have created the epidemic of polio, they cannot stop the program. In a recent article it was pointed out that this is the most deranged reasoning, since more vaccines will mean more vaccine-related cases of polio. But then, "vaccinologists" have difficulty with these "uncertainties". (Jacob JT. A developing country perspective on vaccine-associated paralytic poliomyelitis. Bulletin WHO 2004; 82:53-58. See commentary by D.M. Salisbury at the end of the article.)

Then Dr. Johnson again emphasizes the philosophy that the health of children is secondary to "the program" when he says, **"We saw some compelling data that delaying the birth dose of HepB vaccine would lead to significant disease burden as a consequence of missed opportunity to immunize."** This implies that our children would be endangered from the risk of hepatitis B should the vaccine program stop vaccinating newborns with the HepB vaccine.

In fact, this statement is not based on any risk to U.S. children at all and he makes that plain when he states, **"that the potential impact on countries that have 10% to 15% newborn hepatitis B exposure risk was very distressing to consider."** (page 18) In other words the risk is not to normal U.S. children but to children in developing countries. In fact, hepatitis B is not a risk until the teenage years and after in this country. The only at-risk children are those born to drug abusing parents, to mothers infected with hepatitis B, or to HIV infected parents.

Infectious disease authorities know that 90% of people infected with this virus either have a mild infection and recover or have no symptoms at all. Even pregnant women infected with the virus have only a 20% chance of transmitting the virus to their babies. According to statistics, the United States has one of the lowest rates of hepatitis B infection in the world, with only 53 cases of the infection being reported in children among 3.9 million births. In fact, there were three times as many serious complications from the vaccine as there were children who contracted the disease. The real reason for vaccinating the newborns is to capture them before they can escape the *vaccinologists'* vaccine program.

This is a tactic often used to scare mothers into having their children vaccinated. For example, vaccinologists say that if children are not vaccinated against measles, millions of children could die during a measles epidemic. They know this is nonsense. What they are using are examples taken from developing countries with poor nutrition and poor immune function in which such epidemic death can occur. In the United States we would not see this because of better nutrition, better health facilities and better sanitation. In fact, most deaths seen during measles outbreaks in the United States occur in children in whom vaccination was contraindicated, when the vaccine did not work or in children with chronic, immune-suppressing diseases.

In fact, most studies show that children catching the measles or other childhood diseases have been either fully immunized or partially immunized. The big secret among "vaccinologists" is that anywhere from 20 to 50% of children are not resistant to the diseases for which they have been vaccinated.

Also on page 18, Dr. Johnson tells the committee that it was Dr. Walter Orenstein who **"asked the most provocative question which introduced a great deal of discussion. That was, should we try to seek neurodevelopmental outcomes from children exposed to varying doses of mercury by utilizing the Vaccine Safety Datalink data from one or more sites."** (page 18)

I take from this no one had ever even thought of looking at the data that had just been sitting there all these years unreviewed. Children could have been dropping like flies or suffering from terrible neurodevelopmental defects caused by the vaccine program and no one in the government would have known. In fact, that is exactly what the data suggested was happening, at least as regards neurodevelopmental delays.

We should also appreciate that the government sponsored two conferences on the possible role of metals, aluminum and mercury, being use in vaccines, without any change in vaccine policy occurring after the meetings. These meetings were held a year before this year's 2000 meeting and before any examination of the data which was being held tightly by the CDC (which was denied to other independent, highly qualified researchers). I will talk more about what was discussed in the aluminum conference later. It is very important and is only briefly referred to in this conference for a very good reason. If the public knew what was discussed at the aluminum meeting no one would ever get a vaccination using the presently manufactured types of vaccines again.

Despite what was discussed in the aluminum meeting and the scientific literature on the neurotoxicity of aluminum, Dr. Johnson makes the following remark; **"Aluminum salts have a very wide margin of safety. Aluminum and mercury are often simultaneously administered to infants, both at the same site and at different sites."** Also on page 20, he states, **"However, we also learned that there is absolutely no data, including animal data, about the potential for synergy, additively or antagonism, all of which can occur in binary metal mixtures…"**

It is important here to appreciate a frequently used deception by those who are trying to defend an indefensible practice. They use the very same language just quoted, that is, that there is no data to show, etc., etc. They intend it to convey the idea that the issue has been looked at and studied thoroughly and no toxicity was found. In truth, it means that no one has looked at

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this possibility and there have been no studies that would give us an answer one way or the other.

In fact, we know that aluminum is a significant neurotoxin and that it shares many common mechanisms with mercury as a neurotoxin. For example, they are both toxic to neuronal neurotubules, interfere with antioxidant enzymes, poison DNA repair enzymes, interfere with mitochondrial energy production, block the glutamate reuptake proteins (GLT-1 and GLAST), bind to DNA and interfere with neuronal membrane function. Toxins that share toxic mechanisms are almost always additive and frequently synergistic in their toxicity. So, Dr. Johnson's statement is sheer nonsense.

A significant number of studies have shown that both of these metals play a significant role in all of the neurodegenerative disorders. It is also important to remember, both of these metals accumulate in the brain and spinal cord. This makes them accumulative toxins and therefore much more dangerous than rapidly excreted toxins.

To jump ahead, on page 23 Dr. Tom Sinks, Associate Director for Science at the National Center for Environmental Health at the CDC and the Acting Division Director for Division of Birth Defects, Developmental Disabilities and Health, asks, **"I wonder is there a particular health outcome that is related to aluminum salts that may have anything that we are looking at today?"** Dr. Martin Meyers, Acting Director of the National Vaccine Program Office, answers**, "No, I don't believe there are any particular health concerns that were raised."** This is after an aluminum conference held the previous year that did, indeed, find significant health concerns and extensive scientific literature showing aluminum to be of great concern.

On page 24 Dr. William Weil, a pediatrician representing the Committee on Environmental Health of the American Academy of Pediatrics, brings some sense to the discussion by reminding them that, **"there are just a host of neurodevelopmental data that would suggest that we've got a serious problem. The earlier we go, the more serious the problem."** Here he means that the further back you go during the child's brain development, the more likely the damage to the infant. I must give him credit; at least he briefly recognized that a significant amount of brain development does take place later—that is after birth. He also reminds his collogues that aluminum produced severe dementia and death in dialysis cases. He concludes by saying, **"To think there isn't some possible problem here is unreal."** (page 25)

Not to let it end there, Dr. Meyers adds, **"We held the aluminum meeting in conjunction with the metal ions in biology and medicine meeting, we were quick to point out that in the absence of data we didn't know about additive or inhibitory activities."** Once again we see the "no data" ploy. There is abundant data on the deleterious effects of aluminum on the brain, a significant portion of which came out in that very meeting.

Dr. Johnson also quotes Dr. Thomas Clarkson, who identifies himself as associated with the mercury program at the University of Rochester, as saying that delaying the HepB vaccine for 6 months or so would not affect the mercury burden (page 20). He makes the correct conclusion when he says, **"I would have thought that the difference was in the timing. That is you are protecting the first six months of the developing central nervous system."**

Hallelujah, for a brief moment I thought that they had stumbled on one of the most basic concepts in neurotoxicology. Then Dr. Meyers dashed my hopes by saying that single, separated doses would not affect blood levels at all. At this juncture, we need a little enlightenment. It is important to appreciate that mercury is a fat soluble metal. That is, it is stored in the body's fat. The brain contains 60% fat and therefore is a common site for mercury storage. Now, they establish in this discussion that about half of methylmercury is excreted over several months when ingested. A recent study found that ethylmercury has a half-life of 7 days.

A significant proportion of the mercury will enter the brain (it has been shown to easily pass through the blood-brain barrier) where it is stored in the phospholipids (fats). It should also be appreciated that when cleared from the blood, the ethylmercury enters the bowel, where it is re-circulated many times over—each time depositing more mercury in the child's brain.

With each new vaccine dose, and remember, at the time of this conference, these children were receiving as many as 36 doses of these vaccines by age 2 years, many of which contained mercury—another increment of mercury is added to the brain storage depot. This is why we call mercury an accumulative poison. They never once, not once, mention this vital fact throughout the entire conference. Not once. Moreover, they do so for a good reason; it gives the unwary, those not trained in neuroscience, assurance that all that matters here is blood levels.

In fact, on page 163, Dr. Robert Brent, a developmental biologist and pediatrician at Thomas Jefferson University and Dupont Hospital for Children, says that we don't have data showing accumulation and **"that with the multiple exposures you get an increasing level, and we don't know whether that is true or not."** He redeems himself somewhat by pointing out that some of the damage is irreversible and with each dose more irreversible damage occurs and in that way it is accumulative.

On page 21 Dr. Thomas Clarkson makes the incredible statement implying that he knows of no studies that show exposure to mercury after birth or at six months would have deleterious effects. Dr. Isabelle Rapin, a neurologist for children at Albert Einstein College of Medicine, follows up by saying that **"I am not an expert on mercury in infancy"** but she knows it can affect the nerves (peripheral nervous system). So, here is one of our experts admitting that she knows little about the effects of mercury on the infant. My question is: Why is she here? Dr. Rapin is a neurologist for children at Albert Einstein College of Medicine who stated that she has a keen interest in developmental disorders, in particular those involving language and autism, yet she knows little about the effects of mercury on the infant brain.

This conference is concerned with the effects of mercury in the form of Thimerosal on infant brain development, yet throughout this conference our experts, especially the "vaccinologists", seem to know little about mercury except limited literature that shows no toxic effects except at very high levels. None of the well known experts were invited, such as Dr. Michael Aschner from Bowman Grey School of Medicine or Dr. Boyd Haley, who has done extensive work on the toxic effects

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of low concentrations of mercury on the CNS (Central Nervous System). They were not invited because they would be harmful to the true objective of this meeting, and that was to exonerate mercury in vaccines.

Several times throughout this conference, Dr. Brent reminds everyone that the most sensitive period for the developing brain is during the early stages of pregnancy. In fact, he pinpoints the 8th to 18th week as the period of neuromaturation. In fact, the most rapid period of brain maturation, synaptic development and brain pathway development, is during the last three months of pregnancy continuing until two years after birth. This is often referred to as the **"brain growth spurt".** This is also not mentioned once in this conference, again because if mothers knew that their child's brain was busy developing for up to two years after birth, they would be less likely to accept this safety of mercury nonsense these "vaccinologists" proclaim.

The brain develops over 100 trillion synaptic connections and tens of trillions of dendritic connections during this highly sensitive period. Both dendrites and synapses are very sensitive, even to very low doses of mercury and other toxins. It has also been shown that subtoxic doses of mercury can block the glutamate transport proteins that play such a vital role in protecting the brain against excitotoxicity. Compelling studies indicate that damage to this protective system plays a major role in most of the neurodegenerative diseases and abnormal brain development as well.

Recent studies have shown that glutamate accumulates in the brains of autistic children, yet these experts seem to be unconcerned about a substance (mercury) that is very powerful in triggering brain excitotoxicity.

It is also interesting to see how many times Dr. Brent emphasizes that we do not know the threshold for mercury toxicity for the developing brain. Again, that is not true. We do know and the *Journal of Neurotoxicology* states that anything above 10μg (micrograms) is neurotoxic. The WHO in fact states that there is no safe level of mercury.

On page 164 Dr. Robert Davis, Associate Professor of Pediatrics and Epidemiology at the University of Washington, makes a very important observation. He points out that in a population like the United States you have individuals with varying levels of mercury from other causes (diet, living near coal-burning facilities, etc.) and by vaccinating everyone you raise those with the highest levels even higher and bring those with median levels into a category of higher levels. The "vaccinologists" with their problem of "concrete thinking" cannot seem to appreciate the fact that not everyone is the same. That is, they fail to see these "uncertainties".

To further emphasize this point, let's consider a farming family that lives within three miles of a coal-burning electrical plant. Since they also live near the ocean they eat seafood daily. The fertilizers, pesticides and herbicides used on the crops contain appreciable levels of mercury. The coal-burning electrical plant emits high levels of mercury in the air they breathe daily and the seafood they consume has levels of mercury higher than EPA safety standards. This means that any babies born to these people will have very high mercury levels.

Once born, they are given numerous vaccines containing even more mercury, thereby adding significantly to their already high mercury burden. Are these "vaccinologists" trying to convince us that these children don't matter and that they are to be sacrificed at the alter of "vaccine policy"?

Recent studies by neurotoxicologists have observed that as our ability to detect subtle toxic effects improves, especially on behavior and other neurological functions, we lower the level of acceptable exposure. In fact, Dr. Sinks brings up that exact point, using lead as an example. He notes that as our neurobehavioral testing improved, we lowered the acceptable dose considerably and continue to do so. Dr. Johnson had the audacity to add, "**The smarter we get, the lower the threshold**." Yet, neither he, nor the other participants seem to be getting any smarter concerning this issue.

Dr. Robert Chen, Chief of Vaccine Safety and Development at the National Immunization Program at the CDC, then reveals why they refuse to act on this issue. He says, **"the issue is that it is impossible, unethical to leave kids unimmunized, so you will never, ever resolve that issue. So then we have to refer back from that. "** (page 169) In essence, immunization of the kids takes precedence over safety concerns with the vaccines. If the problem of vaccine toxicity cannot be solved, he seems to be saying, then we must accept that some kids will be harmed by the vaccines. In fact, we are now seeing that the harm from the vaccines exceeds the benefit of disease prevention.

Dr. Brent makes the statement that he knows of no known genetic susceptibility data on mercury and therefore assumes there is a fixed threshold of toxicity. That is, that everyone is susceptible to the same dose of mercury and there are no genetically hypersensitive groups of people. In fact, a recent study found just such a genetic susceptibility in mice. In this study researchers found that mice susceptible to autoimmunity developed neurotoxic effects to their hippocampus, including excitotoxicity, not seen in other strains of mice. They even hypothesize that the same may be true in humans, since familial autoimmunity increases the likelihood of autism in offspring. (Hornig M, Chian D, Lipkin WI. Neurotoxic effects of postnatal Thimerosal are mouse strain dependent. Mol Psychiatry 2004 Sep.;9(9):833–45).

For the next quotation you need a little discussion to be able to appreciate the meaning. They are discussing the fact that in Dr. Verstraeten's study frightening correlations were found between the higher doses of Thimerosal and problems with neurodevelopment, including ADD and autism. The problem with the study was that there were so few children that had been administered Thimerosal-free vaccines, that a true control group could not be used. Instead they had to use children getting 12.5μg of mercury as the control and some even wanted to use the control dose as 37.5μg. So the controls had mercury levels that could indeed cause neurodevelopmental problems. Even with this basic flaw, a strong positive correlation was found between the dose of mercury given and these neurodevelopmental problems.

It was proposed that a group of children receiving non-Thimerosal vaccines be compared to those who had Thimerosal. In fact, we later learn that a large group of children could have been used as a Thimerosal-free control. It seems that for two years before this conference, the Bethesda Naval Hospital had been using unlicensed reduced-Thimerosal vaccines in place of the U.S.-licensed Thimerosal-preserved vaccines to immunize their outpatient children. Unfortunately, in general,

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these children were too young for the symptoms of neurodevelopmental-regressive autism to be manifest when Verstraten began his studies in the late 1990s.

So, now to the quote: Dr. Braun responds to the idea of starting a new study using such Thimerosal-free controls by saying, **"Sure we will have the answer in five years. The question is what can we do now with the data we have?"** (page 170) Well, we have the answer to that, they simply covered this study up, declared that Thimerosal is of no concern and continued the unaltered policy. That is, they can suggest that the pharmaceutical manufacturers of vaccines remove the Thimerosal but not make it mandatory or examine the vaccines to make sure they have removed it.

Let us take a small peek at just how much we can trust the pharmaceutical manufacturers to do the right thing. Several reports of major violations of vaccine manufacturing policy have been cited by the regulatory agencies. This includes obtaining plasma donations without taking adequate histories on donors as to disease exposures and previous health problems, poor record keeping on these donors, improper procedures, and improper handing of specimens.

That these are not minor violations is emphasized by the discovery that a woman with variant Mad Cow Disease was allowed to give plasma to be used in vaccines in England. In fact, it was learned only after the contaminated plasma was pooled and used to make millions of doses of vaccines that her disease was discovered. British health officials told the millions of vaccinated not to worry, since the "experts" have no idea if it will really spread the disease.

Contamination of vaccines is a major concern in this country as well, as these regulatory violations make plain. It is also important to note that no fines were given, just warnings.

Conclusions by the study group

At the end of the conference, a poll was taken asking two questions. One was, Do you think that there is sufficient data to make a causal connection between the use of Thimerosal-containing vaccines and neurodevelopmental delays? Second, do you think further study is called for based on this study?

First, let us see some of the comments on the question of doing further studies. Dr. Paul Stehr-Green, Associate Professor of Epidemiology at the University of Washington School of Public Health and Community Medicine, who voted yes, gave as his reason, **"The implications are so profound these should be examined further."** (page 180) Meanwhile, Dr. Brent interjects his concern that the lawyers will get hold of this information and begin filing lawsuits. He says, **"They want business and this could potentially be a lot of business."** (page 191)

Dr. Loren Koller, Pathologist and Immunotoxicologist at the College of Veterinary Medicine, Oregon State University, is to be congratulated for recognizing more is involved in the vaccine effects than just ethylmercury (page 192). He mentions aluminum and even the viral agents beings used as other possibilities. This is especially important in the face of Dr. R. K. Gherardi's identification of macrophagic myofascitis, a condition causing profound weakness and multiple neurological syndromes, one of which closely resembled multiple sclerosis. Both human studies and animal studies have shown a strong causal relationship to the aluminum hydroxide or aluminum phosphate used as vaccine adjuvants. More than 200 cases have been identified in European countries and the United States and have been described as an "emerging condition".

Here are some of the neurological problems seen with the use of aluminum hydroxide and aluminum phosphate in vaccines. In two children aged 3 and 5 years, doctors at the All Children's Hospital in St. Petersburg, Florida described chronic intestinal pseudo-obstruction, urinary retention, and other findings indicative of a generalized loss of autonomic nervous system function (diffuse dysautonomia). The 3-year old had developmental delay and hypotonia (loss of muscle tone). A biopsy of the children's vaccine injection site disclosed elevated aluminum levels.

In a study of some 92 patients suffering from this emerging syndrome, eight developed a full-blown demyelinating CNS disorder (i.e., multiple sclerosis) [Authier FJ, Cherin P, *et al.* Central nervous system disease in patients with macrophagic myofasciitis. Brain 2001;124:974–83]. This included sensory and motor symptoms, visual loss, bladder dysfunction, cerebellar signs (loss of balance and coordination) and cognitive (thinking) and behavioral disorders.

Dr. Gherardi, the French physician who first described the condition in 1998, has collected over 200 proven cases. One third of these developed an autoimmune disease such as multiple sclerosis. Of critical importance is his finding that even in the absence of obvious autoimmune disease there is evidence of chronic immune stimulation caused by the injected aluminum, known to be a very powerful immune adjuvant.

The reason this is so important is that there is overwhelming evidence that chronic immune activation in the brain (activation of microglial cells in the brain) is a major cause of damage in numerous degenerative brain disorders, from multiple sclerosis to the classic neurodegenerative diseases (Alzheimer's disease, Parkinson's and ALS). In fact, I have presented evidence that chronic immune activation of CNS microglia is a major cause of autism, attention deficit disorder and Gulf War Syndrome.

Dr. Gherardi emphasizes that once the aluminum is injected into the muscle, the immune activation persists for years. In addition, we must consider the effect of the aluminum that travels to the brain itself. Numerous studies have shown harmful effects when aluminum accumulates in the brain. A growing amount of evidence points to high brain aluminum levels as a major contributor to Alzheimer's disease and possibly Parkinson's disease and ALS (Lou Geherig's disease). This may also explain the 10X increase in Alzheimer's disease in those receiving the flu vaccine 5 years in a row. (Dr. Hugh Fudenberg, in press, Journal of Clinical Investigation). It is also interesting to note that a recent study found that aluminum phosphate produced a 3X elevation in blood levels of aluminum, as did aluminum hydroxide (Flarend RE, Hem SL, *et al.* In vivo absorption of aluminum-containing vaccine adjuvants using 26Al. Vaccine 1997 Aug.-Sept.;15:1314–8).

Of course, in this conference, our illustrious experts tell us that there is "no data showing an additive or synergistic effect between mercury and aluminum."

Dr. Rapin expressed her concern over public opinion when this information eventually gets out. She says (page 197), they

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are going to be captured by the public and we had better make sure that **"(a) we counsel them carefully and (b) that we pursue this because of the very important public health and public implications of the data."** Dr. Johnson adds, **"the stakes are very high…."** From this, how can one conclude anything other than the fact that at least these scientists were extremely concerned by what was discovered by this study examining the Vaccine Safety Datalink material? They were obviously terrified that the information would leak out to the public. Stamped in bold letters at the top of each page of the study were the words: "DO NOT COPY OR RELEASE" and "CONFIDENTIAL".

This is not the wording one would expect on a clinical study of vaccine safety; rather you would expect it on top-secret NSA or CIA files. Why was this information being kept secret? The answer is obvious—it might endanger the vaccine program and indict the federal regulatory agencies for ignoring this danger for so many years. Our society is littered with millions of children who have been harmed in one degree or another by this vaccine policy. In addition, let us not forget the millions of parents who have had to watch helplessly as their children have been destroyed by this devastating vaccine program.

Dr. Bernier on page 198 says, **"the negative findings need to be pinned down and published."** Why was he so insistent that the **"negative findings"** be published? Because he said, **"other less responsible parties will treat this as a signal."** By that he means, a signal of a problem with Thimerosal-containing vaccines. From this, I assume he wants a paper that says only that nothing was found by the study. As we shall see, he gets his wish.

In addition, on page 198, Dr. Rapin notes that a study in California found a 300X increase in autism following the introduction of certain vaccines. She quickly attributes this to better physician recognition. Two things are critical to note at this point. She makes this assertion on better physician recognition without any data at all, just her wishful thinking. If someone pointing out the dangers of vaccines were to do that, she would scream "junk science".

Second, Dr. Weil on page 207, attacks this reasoning when he says, **"the number of dose related relationships are linear and statistically significant. You can play with this all you want. They are linear. They are statistically significant."** In other words, how can you argue with results that show a strong dose/response relationship between the dose of mercury and neurodevelopmental outcomes? The higher the mercury levels in the children the greater the number of neurological problems. He continues by saying that the increase in neurobehavioral problems is probably real. He tells them that he works in a school system with special education programs and **"I have to say the number of kids getting help in special education is growing nationally and state by state at a rate not seen before. So there is some kind of increase. We can argue about what it is due to."** (page 207)

Dr. Johnson seems to be impressed by the findings as well. He says on page 199, **"This association leads me to favor a recommendation that infants up to two years old not be immunized with Thimerosal-containing vaccines if suitable alternative preparations are available."** Incredibly, he quickly adds, **"I do not believe the diagnosis justifies compensation in the Vaccine Compensation Program at this point."** It is interesting to note that one of our experts in attendance is Dr. Vito Caserta, the Chief Officer for the Vaccine Injury Compensation Program.

At this point Dr. Johnson tells the group of his concerns for his own grandchild. He says, (page 200) **"Forgive this personal comment, but I got called out at eight o'clock for an emergency call and my daughter-in-law delivered a son by C-section. Our first male in the line of the next generation and I do not want that grandson to get a Thimerosal-containing vaccine until we know better what is going on. It will probably take a long time. In the meantime, and I know there are probably implications for this internationally, but in the meanwhile I think I want that grandson to only be given Thimerosal-free vaccines."**

So, we have a scientist sitting on this panel which will eventually make policy concerning all of the children in this country, as well as other countries, who is terrified about his new grandson getting a Thimerosal-containing vaccine but he is not concerned enough about your child to speak out and try to stop this insanity. He allows a cover-up to take place after this meeting adjourns and remains silent.

It is also interesting to note that he feels the answers will be a long time coming, but in the mean time, his grandson will be protected. The American Academy of Pediatrics, The American Academy of Family Practice, the AMA, CDC and every other organization will endorse these vaccines and proclaim them to be safe as spring water, but Dr. Johnson and some of the others will keep their silence.

It is only during the last day of the conference that we learn that most of the objections concerning the positive relationship between Thimerosal-containing vaccines and ADD and ADHD were bogus. For example, Dr. Rapin on page 200 notes that all children in the study were below age 6 and that ADD and ADHD are very difficult to diagnose in pre-schoolers. She also notes that some children were followed for only a short period.

Dr. Stein adds that in fact the average age for diagnosis of ADHD was 4 years and 1 month, a very difficult diagnosis to make with the guidelines, as published by the American Academy of Pediatrics, limiting diagnosis to 6 to 12 year olds. Of course, he was implying that too many were diagnosed as ADHD. Yet, a recent study found that the famous Denmark study that led to the announcement by the Institute of Medicine that there was no relationship between autism and the MMR vaccine, used the same tactic. They cut off the age of follow-up at age six.

It is known that many cases appear after this age group, especially with ADD and ADHD. In fact, most learning problems appear as the child is called on to handle more involved intellectual material. Therefore, the chances are that they failed to diagnose a number of cases by stopping the study too early.

Several of the participants tried to imply that autism was a genetic disorder and therefore could have nothing to do with vaccines. Dr. Weil put that to rest with this comment, **"We don't see that kind of genetic change in 30 years."** In other words, how can we suddenly see a 300% increase in a genetically related disorder over such a short period? It is also known that there are two forms of autism, one that is apparent at birth and one that develops later in childhood. The former has not

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changed in incidence since statistics have been kept; the other is epidemic.

One interesting exchange, which involves two studies in children born to mothers consuming high intakes of mercury-contaminated fish, ends up providing their justification for the view that mercury is of no danger to children vaccinated with vaccines containing Thimerosal. One study in the journal *Neurotoxicology*, examined children living in the Republic of Seychelles. This study examined the effect of prenatal exposure to mercury through the mother's consumption of fish high in methylmercury,

A battery of developmental milestone tests were done and no adverse effects were reported in the study done by Dr. Clarkson and co-workers, the very same person in this conference. He never mentions that a follow-up study of these same children did find a positive correlation between methylmercury exposure and poor performance on a memory test. In a subsequent study of children living on the Faroe Islands exposed to methylmercury, researchers also found impairments of neurodevelopment. This experiment was done by scientists from Japan.

Throughout the remainder of this discussion, Dr. Clarkson and others refer to these two studies. When they are reminded that the Faroe study did find neurological injury to the children, they counter by saying that this was prenatal exposure to mercury and not exposure following birth as would be seen with vaccination. The idea being that prenatally the brain is undergoing neural formation and development making it more vulnerable. As I have mentioned, this rapid brain growth and development continues for two years after birth and even at age 6 years the brain is only 80% formed.

Dr. Clarkson keeps referring to the Seychelles study which demonstrated that the children reached normal neurodevelopmental milestones as shown by a number of tests. Dr Weil points out on page 216 that this tells us little about these children's future brain function. He says, **"I have taken a lot of histories of kids who are in trouble in school. The history is that developmental milestones were normal or advanced and they can't read at second grade, they can't write at third grade, they can't do math in the fourth grade and it has no relationship as far as I can tell to the history we get of the developmental milestones. So I think this is a very crude measure of neurodevelopment."**

In other words, both of these studies tell us nothing about the actual development of these children's brain function except that they reached the most basic of milestones. To put this another way, your child may be able to stack blocks, recognize shapes and have basic language skills, but later in life he/she could be significantly impaired when it came to higher math, more advanced language skills (comprehension) and ability to compete in a very competitive intellectual environment, like college or advanced schooling. The future of such children would be limited to the more mundane and intellectually limited jobs.

Postnatal brain development, that is from birth to age six or seven, involves the fine tuning of synaptic connections, dendritic development and pathway refinement, all of which prepare the brain for more complex thinking. These brain elements are very sensitive to toxins and excessive immune stimulation during this period. This fact is never mentioned at the conference.

In addition, it must be remembered that the children in these two studies were exposed only to methylmercury and not the combined neurotoxic effect of mercury, aluminum and excessive and chronic activation of the brain's immune system (microgia). This is what makes it so incredible, that several of these "vaccinologists" and so-called experts would express doubt about the "biological plausibility" of Thimerosal or any vaccine component causing neurodevelopmental problems. The medical literature is exploding with such studies. The biological plausibility is very powerful.

Mercury, for example, even in low concentrations, is known to impair energy production by mitochondrial enzymes. The brain has one of the highest metabolic rates of any organ and impairment of its energy supply, especially during development, can have devastating consequences. In addition, mercury, even in lower concentrations, is known to damage DNA and impair DNA repair enzymes, which again plays a vital role in brain development. Mercury is known to impair neurotubule stability, even in very low concentrations. Neurotubules are absolutely essential to normal brain cell function. Mercury activates microglial cells, which increases excitotoxicity and brain free radical production as well as lipid peroxidation, central mechanisms in brain injury. In addition, even in doses below that which can cause obvious cell injury, mercury impairs the glutamate transport system, which in turn triggers excitotoxicity, a central mechanism in autism and other neurological disorders. Ironically, aluminum also paralyzes this system.

On page 228, we see another admission that the government has had no interest in demonstrating the safety of Thimerosal-containing vaccines despite over 2000 articles showing harmful effects of mercury. Here we see a reference to the fact that the FDA **"has a wonderful facility in Arkansas with hundreds of thousands of animals"** available for any study needed to supply these answers on safety. The big question to be asked is – So, why has the government ignored the need for research to answer these questions concerning Thimerosal safety? You will recall in the beginning the participants of this conference complained that there were just so few studies or no studies concerning this "problem".

Again, on page 229 Dr, Brent rails about the lawsuit problem. He tells the others that he has been involved in three lawsuits related to vaccine injuries leading to birth defects and concluded, **"If you want to see junk science, look at those cases…."** He then complains about the type of scientists testifying in these cases. He adds, **"But the fact is those scientist are out there in the United States."** In essence, he labels anyone who opposes the "official policy" on vaccines as a junk scientists. We have seen in the discussion who the "junk scientists" really are.

Knowing that what they have found can cause them a great deal of problems he adds, **"The medical/legal findings in this study, causal or not, are horrendous…. If an allegation was made that a child's neurobehavioral findings were caused by Thimerosal-containing vaccines, you could readily find a junk scientist who will support the claim with a reasonable degree of certainty."** On page 229 he then admits that they are

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in a bad position because they have no data for their defense. Now, who are the junk scientists?

Is a "real scientist" one who has no data, just wishful thinking and a "feeling" that everything will be all right? Are real scientists the ones who omit recognized experts on the problem in question during a conference because it might endanger the "program"? Are they the ones who make statements that they don't want their grandson to get Thimerosal-containing vaccines until the problem is worked out, but then tell millions of parents that the vaccines are perfectly safe for their children and grandchildren?

Dr. Meyers on page 231 put it this way, **"My own concern, and a couple of you said it, there is an association between vaccines and outcomes that worries both parents and pediatricians."** He sites other possible connections to vaccine-related neurobehavioral and neurodevelopmental problems including the number of vaccines being given, the types of antigens being used, and other vaccine additives.

Dr. Caserta tells the group that he attended the aluminum conference the previous year and learned that metals could often act differently in biological systems when existing as an ion. This is interesting in the face of the finding that fluoride when combined to aluminum forms a compound that can destroy numerous hippocampal neurons at a concentration of 0.5 ppm in drinking water. It seems that aluminum readily combines with fluoride to form this toxic compound. With over 60% of communities having fluoridated drinking water this becomes a major concern.

It has also been learned that fluoroaluminum compounds mimic the phosphate and can activate G-proteins. G-proteins play a major role in numerous biological systems, including endocrine, neurotransmitters, and as cellular second messengers. Some of the glutamate receptors are operated by a G-protein mechanism.

Over the next ten to fifteen pages, they discuss how to control this information so that it will not get out and if it does how to control the damage. On page 248 Dr. Clements has this to say: **"But there is now the point at which the research results have to be handled, and even if this committee decides that there is no association and that information gets out, the work has been done and through the freedom of information that will be taken by others and will be used in other ways beyond the control of this group. And I am very concerned about that as I suspect that it is already too late to do anything regardless of any professional body and what they say."**

In other words, he wants this information kept not only from the public but also from other scientists and pediatricians until they can be properly counseled. In the next statement he spills the beans as to why he is determined that no outsider get hold of this damaging information. He says, **"My mandate as I sit here in this group is to make sure at the end of the day that 100,000,000 are immunized with DTP, Hepatitis B and if possible Hib, this year, next year, and for many years to come, and that will have to be with Thimerosal-containing vaccines unless a miracle occurs and an alternative is found quickly and is tried and found to be safe."**

This is one of the most shocking statements I have ever heard. In essence, he is saying, I don't care if the vaccines are found to be harmful and destroying the development of children's brains, these vaccines will be given now and forever. His only concern, by his own admission, is to protect the vaccine program even if it is not safe. Dr. Brent refers to this as an **"eloquent statement."**

On page 253, we again see that these scientists have a double standard when it comes to their children and grandchildren. Dr. Rapin raises the point about a loss of an IQ point caused by Thimerosal exposure. She says, **"Can we measure the IQ that accurately, that this one little point is relevant?"** Then she answers her own question by saying, **"Even in my grandchildren, one IQ point I am going to fight about."** Yet, they are saying in unison, in essence—"To hell with your children"—to the rest of America.

It is also interesting that they bring up the history of lead as a neurobehavioral toxin. Dr. Weil noted that the neurotoxicologists and regulatory agencies have lowered the acceptable level from 10 to 5μg. In fact, some feel that even lower levels are neurotoxic to the developing brain. Before the toxicologists began to look at lead as a brain toxin in children most "experts" assumed it was not toxic even at very high levels. Again, it shows that "experts" can be wrong and it is the public who pays the price.

Dr. Chen on page 256 expresses his concern about this information reaching the public. He remarks, **"We have been privileged so far that given the sensitivity of information, we have been able to manage to keep it out of, let's say, less responsible hands…."** Dr. Bernier agrees and notes, **"This information has been held fairly tightly."** Later he calls it **"embargoed information"** and **"very highly protected information."**

That they knew the implications of what they had discovered was illustrated by Dr. Chen's statement on page 258. He says, **" I think overall there was this aura that we were engaged in something as important as anything else we have ever done. So I think that this was another element to this that made this a special meeting."** You may remember, Dr. Weil emphasized that the data analysis left no doubt that there was a strong correlation between neurodevelopmental problems and exposure to Thimerosal-containing vaccines. So if they understood the importance of this finding and this was the most important thing they have ever dealt with, why was this being kept from the public? In fact, it gets even worse.

Just so you will not doubt my statement that this audience of experts was not objective, I give you the words of Dr. Walter Orenstein, Director of the National Immunization Program at the CDC, on page 259. He tells the group, **"I have seen him (Verstraeten) in audience after audience deal with exceedingly skeptical individuals…."** "Exceedingly skeptical individuals" does that sound like objective scientists who wanted to look at the data with a clear mind, or were they scientists who were convinced before the meeting was held that there was no danger to children from Thimerosal or any other vaccine component?

In one of the closing remarks (page 257) Dr. Bernier says, **"the other thing I was struck by was the science"**, meaning the science expressed by the attendees of the meeting. Then Dr, Orenstein adds, **"I would also like to thank Roger Bernier who pulled off this meeting in rather short notice..."** Here is

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a meeting that has been called one of the most important they have ever dealt with and we learn that it was "pulled off" on short notice. In addition, we were told that the results of this meeting would lead to eventual vaccine policy. He then has the nerve to add: **"In a sense this meeting addresses some of the concerns we had last summer when we were trying to make policy in the absence of a careful scientific review. I think this time we have gotten it straight."**

Well, I hate to be the one to break the news, but he didn't get it straight. There was little or no science in this meeting; rather it was composed of a lot of haggling and nit picking over epidemiological methodology and statistical minutia in an effort to discredit the data, all without success. In fact, the so-called mercury experts admitted they had to do some quick homework to refresh their memories and learn something about the subject.

Conclusions

This top secret meeting was held to discuss a study done by Dr. Thomas Verstraeten and his co-workers using Vaccine Safety Datalink data as a project collaboration between the CDC's National Immunization Program (NIP) and four HMOs. The study examined the records of 110,000 children. Within the limits of the data, they did a very through study and found the following:

1. Exposure to Thimerosal-containing vaccines at one month was associated significantly with the **misery and unhappiness disorder** that was dose related. That is, the higher the child's exposure to Thimerosal the higher the incidence of the disorder. This disorder is characterized by a baby that cries uncontrollably and is fretful more so than that seen in normal babies.

2. A nearly significant increased risk of ADD with 12.5µg exposure at one month.

3. With exposure at 3 months, they found an increasing risk of neurodevelopmental disorders, including speech disorders, with increasing exposure to Thimerosal. This was statistically significant.

It is important to remember that the control group was not children without Thimerosal exposure but, rather, those at 12.5µg exposure. This means that there is a significant likelihood that even more neurodevelopmental problems would have been seen had they used a real control population. No one disagreed that these findings were significant and troubling. Yet, when the final study was published in the journal *Pediatrics*, Dr. Verstraeten and co-workers reported that no consistent associations were found between Thimerosal-containing vaccine exposure and neurodevelopmental problems. In addition, he lists himself as an employee of the CDC, not disclosing the fact that at the time the article was accepted, he worked for GlaxoSmithKline, a vaccine manufacturing company.

So how did they do this bit of prestidigitation? They simply added another HMO to the data: the Harvard Pilgrimage. (Additionally there were other manipulations, e.g., altering inclusion criteria, discarding children receiving the highest total dose, splitting children into separate groups, using only one HMO's data in some cases, expressing effects ratios in terms of per dose of mercury.) Congressman Dave Weldon noted in his letter to the CDC Director that this HMO had been in receivership by the state of Massachusetts because its records were in shambles. Yet, this study was able to make the embarrassing data from Dr. Verstraeten's previous study disappear. Attempts by Congressman Weldon to force the CDC to release the data to an independent researcher, Dr. Mark Geier, a researcher with impeccable credentials and widely published in peer-reviewed journals, have failed and the CDC now claims that the original datsets Verstraeten *et al.* used have been "lost".

It is obvious that a massive cover-up is in progress, as we have seen with so many other scandals, such as fluoride, food-based excitotoxins, pesticides, aluminum, and now vaccines. I would caution those critical of the present vaccine policy not to put all their eggs in one basket, that is, with Thimerosal as being the main culprit. There is no question that it plays a significant role, but there are other factors that are also critical, including aluminum, fluoroaluminum complexes, and chronic immune activation of brain microglia. I believe that repeated, closely spaced, sequential vaccinations given during the most active period of brain development is the major cause of autism.

In fact, excessive, chronic microglial activation can explain many of the effects of excessive vaccine exposure as I point out in two recently published articles. One property of both aluminum and mercury is microglial activation. With chronic microglial activation, large concentrations of excitotoxins are released as well as neurotoxic cytokines. These have been shown to destroy synaptic connections, dendrites and cause abnormal pathway development in the developing brain as well as in the adult brain.

In essence, too many vaccines are being given to children during the brain's most rapid growth period. Known toxic metals are being used in vaccines, interfering with brain metabolism and antioxidant enzymes, damaging DNA and DNA repair enzymes and triggering excitotoxicity. Removing the mercury will help but will not solve the problem because overactivation of the brain's immune system will cause varying degrees of neurological damage to the highly-vulnerable developing brain.

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Marcel de Graaff
Member of the European Parliament
The European Parliament
Bât. ALTIERO SPINELLI - 06E240
Wiertzstraat 60
B-1047 Brussels
Belgium

Also by e-mail:
withdrawnproducts@ema.europa.eu emer.cooke@ema.europa.eu
European Medicines Agency
Domenico Scarlattilaan 6
1083 HS Amsterdam
The Netherlands

Request for the direct suspension of marketing authorizations

Brussels, 4 October 2023

Dear Sir/Madam,

We, the undersigned Members of the European Parliament, want to convey our deep concerns regarding the safety and ineffectiveness of COVID-19 vaccines and we believe it is imperative that immediate and resolute actions should be taken.

We therefore request the direct suspension of the marketing authorizations of the following COVID-19 vaccines:
- Conditional Marketing Authorisation Pfizer (Comirnaty) dated 21 December 2020.[1]
- Conditional Marketing Authorisation Moderna (Spikevax) dated 6 January 2021.[2]
- Renewal of Marketing Authorisation Pfizer (Comirnaty-tozinameran) dated 31 August 2023.[3]
- Renewal Marketing Authorisation Moderna (Spikevax-elasomeran) dated 15 September 2023.[4]

In this letter, we aim to provide a comprehensive, though not exhaustive, rationale for our urgent plea.

Nevertheless, we request you, as a governing body that is legally obligated to take a careful consideration, to broaden your perspective beyond the issues and deficiencies we have cited. The discourse surrounding COVID-19 vaccines has been marked by a disconcerting upsurge in reported side effects, and, astonishingly, there have even been alarming reports of excess mortality. All of this has unfolded beneath a veil of unwarranted secrecy.

Vaccines not authorised for transmission control
As per Article 4.1 of the marketing authorization issued by the European Commission on August 31, 2023, Pfizer-BioNTech's (Comirnaty) vaccines are exclusively approved for active immunization.

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[1] https://ec.europa.eu/health/documents/community-register/2020/20201221150522 /dec_150522_en.pdf
[2] https://ec.europa.eu/health/documents/community-register/ 2021/20210106150575/ dec_150575_en.pdf
[3] https://ec.europa.eu/health/documents/community-register/2023/202308311 60389/dec_160389 _en.pdf
[4] https://ec.europa.eu/health/documents/community-register/2023/2023091 5160561/dec_160561_en.pdf

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Comirnaty 30 micrograms/dose concentrate for dispersion for injection is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

[5]

According to article 4.1 of the marketing authorisation by the European Commission dated 15 September 2023 Moderna (Spikevax-elasomeran) vaccinations are also only authorised for active immunisation only.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.

The use of this vaccine should be in accordance with official recommendations.

[6]

It can be concluded that these therapeutic indications do not align with the fact that these vaccines are being promoted by pharmaceutical companies, politicians, and health professionals due to their potential for transmission control.

As a medicines agency, you are supposed to be well-versed in the intended medical uses of these vaccines. This essentially means that these medicines, including vaccines, should only be administered to individuals who seek personal protection, and they are not authorized for the purpose of reducing transmission or infection rates (transmission control).

As a medicines agency adhering to the principles of good administration and good medical practice, your duty entails the dissemination of this information to healthcare professionals, especially physicians. This enables them to incorporate it into their conversations during the informed consent process, as mandated by both national medical disciplinary laws and medical ethics. It is essential to emphasize that any off-label prescribing must always be performed with the informed consent of the patient.

Clinical trials

Clinical trials for XBB.15 have commenced only recently and are scheduled for completion in 2024. Therefore, it is premature to consider renewing a license at this stage, especially when there is currently no international public health emergency of concern (PHEIC).[7]

Pfizer clinical trial (XBB) 10.08.23 to 28.06.24 (phase 2/3)

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[5] https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

[6] www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf

[7] https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic

Study Overview

Brief Summary:
The purpose of this clinical protocol is to learn about the safety, tolerability, and immunogenicity of new BNT162b2 RNA-based vaccine candidates targeting new variants of SARS-CoV-2 in healthy people.

Substudy A:

- This study will evaluate the safety, tolerability, and immunogenicity of BNT162b2 (Omi **XBB**.1.5) given as a single 30 µg dose,
  - in people who are 12 years of age and older,
  - who previously received at least 3 doses of a US-authorized mRNA COVID-19 vaccine, with...

+ Show more

OFFICIAL TITLE

A PHASE 2/3 PROTOCOL TO INVESTIGATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF BNT162b2 RNA-BASED VACCINE CANDIDATES FOR SARS-CoV-2 NEW VARIANTS IN HEALTHY INDIVIDUALS

CONDITIONS

SARS-CoV-2 Infection | COVID-19

INTERVENTION / TREATMENT

Biological: BNT162b2 (Omi **XBB**.1.5)

STUDY START (ACTUAL)
2023-08-10

PRIMARY COMPLETION (ESTIMATED)
2024-06-28

STUDY COMPLETION (ESTIMATED)
2024-06-28

ENROLLMENT (ESTIMATED)
700

STUDY TYPE
Interventional

PHASE
Phase 2
Phase 3

OTHER STUDY ID NUMBERS
C4591054 [8]

Moderna: 08.03.23 to 31.12.24 (observational phase)

Study Overview

Brief Summary:
The goal of this observational study is to analyze binding antibody levels in adults in the United States (US) after receiving coronavirus disease 2019 (COVID-19) bivalent boosters (original and omicron BA.4/5) and updated COVID-19 vaccines (**XBB**.1.5).

OFFICIAL TITLE

DisCOVEries 2 - An Observational Study to Evaluate the Immunogenicity of mRNA **COVID-19** Bivalent Vaccines (Original and Omicron BA.4/BA.5) and 2023 Updated mRNA **COVID-19** Vaccines (**XBB**.1.5)

CONDITIONS

COVID-19

INTERVENTION / TREATMENT

Biological: Moderna COVID-19 Vaccine
Biological: Moderna mRNA1273.222 Booster
Biological: Pfizer COVID-19 Vaccine
Show 2 more interventions/treatments

STUDY START (ACTUAL)
2023-03-08

PRIMARY COMPLETION (ESTIMATED)
2023-10-01

STUDY COMPLETION (ESTIMATED)
2024-12-31

ENROLLMENT (ESTIMATED)
2850

STUDY TYPE
Observational

OTHER STUDY ID NUMBERS
mRNA-1273-P922 [9]

Main rule for authorisation of GMOs

The main rules for allowing genetically modified organisms (GMOs) in the environment can be found in Articles 6 to 11 of Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.[10] It makes perfect sense that the rules for this are enormously strict as it can have a major impact on humans and the environment.

However, an unusual occurrence transpired on July 15, 2020. In response to the COVID-19 pandemic, a new Regulation was hastily introduced and became effective on July 18, 2020 (refer to Article 5). The key provisions of significance are found in Articles 2(1) together with (2) and 4(1) of Regulation 2020/1043/EU. This regulation pertains to the conduct of clinical trials involving medicinal products designed for human use that contain or consist of genetically modified organisms and are intended for

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[8] https://www.clinicaltrials.gov/study/NCT05997290
[9] https://www.clinicaltrials.gov/study/NCT05765578 Moderna clinical trial (XBB)
[10] https://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC_1&format=PDF

the treatment or prevention of coronavirus disease (COVID-19), as well as the supply of such medicinal products.[11]

Article 2

1. All operations related to the conduct of clinical trials, including packaging and labelling, storage, transport, destruction, disposal, distribution, supply, administration or use of investigational medicinal products for human use containing or consisting of GMOs intended to treat or prevent COVID-19, with the exception of the manufacturing of the investigational medicinal products, shall not require a prior environmental risk assessment or consent in accordance with Articles 6 to 11 of Directive 2001/18/EC or Articles 4 to 13 of Directive 2009/41/EC when these operations relate to the conduct of a clinical trial authorised in accordance with Directive 2001/20/EC.

2. Sponsors shall implement appropriate measures to minimise foreseeable negative environmental impacts resulting from the intended or unintended release of the investigational medicinal product into the environment.

[12]

Article 4

1. This Regulation shall apply as long as WHO has declared COVID-19 to be a pandemic or as long as an implementing act by which the Commission recognises a situation of public health emergency due to COVID-19 in accordance with Article 12 of Decision No 1082/2013/EU of the European Parliament and of the Council (7) applies.

[13]

This Regulation allowed for a temporary derogation from the very strict rules of Directive 2001/18/EC.[14]

Of particular significance are Articles 6 and 9 of the Directive. These articles pertain to the authorization procedure and public consultation and information. It's worth noting that these provisions align with the Aarhus Convention, which focuses on access to information, public participation in decision-making, and access to justice in environmental matters. The Aarhus Convention became effective in the Netherlands on March 29, 2005.[15]

Article 9

Consultation of and information to the public

1. Member States shall, without prejudice to the provisions of Articles 7 and 25, consult the public and, where appropriate, groups on the proposed deliberate release. In doing so, Member States shall lay down arrangements for this consultation, including a reasonable time-period, in order to give the public or groups the opportunity to express an opinion.

2. Without prejudice to the provisions of Article 25:

— Member States shall make available to the public information on all part B releases of GMOs in their territory;

— the Commission shall make available to the public the information contained in the system of exchange of information pursuant to Article 11.

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[11] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32020R1043
[12] Ibidem
[13] Ibidem
[14] https://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC_1&format=PDF
[15] https://wetten.overheid.nl/BWBV0001700/2005-03-29

Article 6

Standard authorisation procedure

1. Without prejudice to Article 5, any person must, before undertaking a deliberate release of a GMO or of a combination of GMOs, submit a notification to the competent authority of the Member State within whose territory the release is to take place.

2. The notification referred to in paragraph 1 shall include:

(a) a technical dossier supplying the information specified in Annex III necessary for carrying out the environmental risk assessment of the deliberate release of a GMO or combination of GMOs, in particular:

(i) general information including information on personnel and training,

(ii) information relating to the GMO(s),

(iii) information relating to the conditions of release and the potential receiving environment,

(iv) information on the interactions between the GMO(s) and the environment,

(v) a plan for monitoring in accordance with the relevant parts of Annex III in order to identify effects of the GMO(s) on human health or the environment,

(vi) information on control, remediation methods, waste treatment and emergency response plans,

(vii) a summary of the dossier;

(b) the environmental risk assessment and the conclusions required in Annex II, section D, together with any bibliographic reference and indications of the methods used.

The main rule is however that a GMO can only receive authorization in the European Union once a technical dossier, which includes seven specified documents, has been submitted, along with an environmental risk assessment.

Recently, a report titled "Resilient Biotechnology Policy: Lessons from the COVID-19 Crisis and Opportunities for Enhancing Resilience in Biotechnology Policy" was issued by the Committee on Genetic Modification (COGEM) on October 11, 2022, and made public on December 16, 2022.[16]

Chapter 3 of this report shows that Regulation 2020/1043/EU is void because it is not based on the correct legal basis. Articles 114 or 168(4)(c) of the Treaty on the Functioning of the European Union (TFEU) cannot be invoked in this case. This means that the rules of Directive 2001/18/EC continued to apply in full and that a technical dossier and an environmental report should therefore have been submitted. Having failed to do so, all the permits issued were thus unlawfully granted to the pharmaceutical companies.

For the 2 extensions, it also applies that even if Regulation 2020/1043 would not be void, then at least according to Article 4(1) of the Regulation, a technical dossier and an environmental risk assessment should have been submitted for the extensions, since the PHEIC was terminated by the WHO on May 5, 2023.

Furthermore, it is imperative that the public be informed and consulted in compliance with Article 9 of the Ordinance. Given that none of these procedures were followed, it highlights the presence of significant procedural errors, making the granted authorisations invalid. Consequently, seeking an extension of the existing license was not the appropriate course of action; instead, a new license application should have been submitted. This underscores the necessity for an immediate suspension of the issued marketing authorizations.

It's worth noting that the same issue also pertains to Regulation 2019/5/EU. This regulation is also based on the wrong legal ground, namely: Articles 114 and 168(4)(c) TFEU. Consequently, this Regulation is also considered void.

Quality of the vaccines

It is evident that vaccines failing to meet quality standards should not be granted marketing authorization. Concerning the development of vaccines, there have been disconcerting reports about their quality. In brief, and without covering all the issues, the following deficiencies can be highlighted.

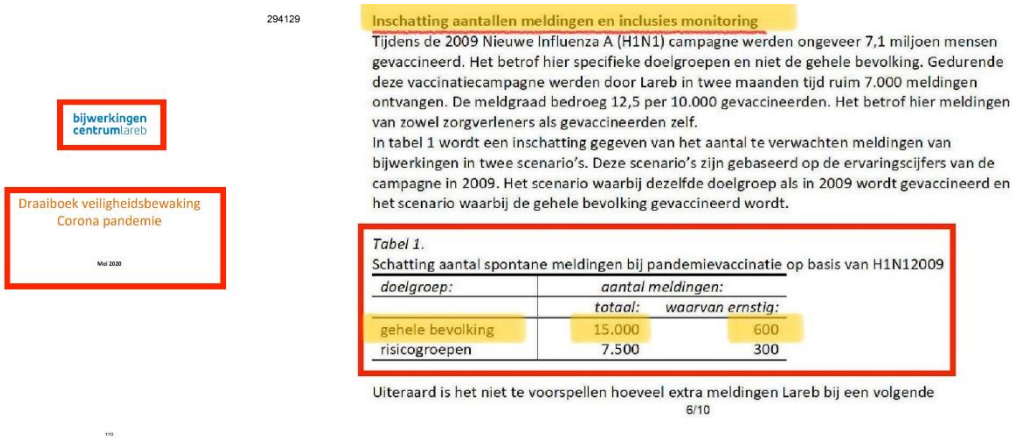
a. The vaccines are harmful

It is evident that the vaccines carry health risks, as substantiated by the substantial volume of reports on adverse reactions received in the Netherlands by the Centre for National Registration and Evaluation of Adverse Reactions (LAREB), as outlined in their report dated September 17, 2023.

[16] https://cogem.net/app/uploads/2022/12/CGM-2022-05-Veerkrachtig-biotechnologiebeleid.pdf

able ducer/Tradename	Total number of reports*	Number of adverse reactions reported	Number of reports with a serious adverse reaction**	Deceased
Pfizer (Comirnaty)	125.746	518.269	3.764	506
Pfizer herhaalprik	2.214	10.413	54	13
Moderna (Spikevax)	49.909	286.598	934	91
Moderna herhaalprik	3.592	17.791	88	12
AstraZeneca (Vaxzevria)	38.033	223.424	997	79
Janssen (Jcovden)	15.101	78.337	291	17
Novavax (Nuvaxovid)	60	277	-	-
Merk onbekend	584	2.439	95	33
Total	**235.239**	**1.137.548**	**6.223**	**751**

This is serious considering that in May 2020, the LAREB prepared a "Corona pandemic safety monitoring plan" in which it assumed that 15,000 reports would be received -600 of which were serious- if the entire population were vaccinated (see page 6 of 10 of the plan).[17]


294129

bijwerkingen centrumLareb

Draaiboek veiligheidsbewaking Corona pandemie

Mei 2020

Inschatting aantallen meldingen en inclusies monitoring

Tijdens de 2009 Nieuwe Influenza A (H1N1) campagne werden ongeveer 7,1 miljoen mensen gevaccineerd. Het betrof hier specifieke doelgroepen en niet de gehele bevolking. Gedurende deze vaccinatiecampagne werden door Lareb in twee maanden tijd ruim 7.000 meldingen ontvangen. De meldgraad bedroeg 12,5 per 10.000 gevaccineerden. Het betrof hier meldingen van zowel zorgverleners als gevaccineerden zelf.
In tabel 1 wordt een inschatting gegeven van het aantal te verwachten meldingen van bijwerkingen in twee scenario's. Deze scenario's zijn gebaseerd op de ervaringscijfers van de campagne in 2009. Het scenario waarbij dezelfde doelgroep als in 2009 wordt gevaccineerd en het scenario waarbij de gehele bevolking gevaccineerd wordt.

Tabel 1.
Schatting aantal spontane meldingen bij pandemievaccinatie op basis van H1N12009

doelgroep:	*aantal meldingen:*	
	totaal:	*waarvan ernstig:*
gehele bevolking	15.000	600
risicogroepen	7.500	300

Uiteraard is het niet te voorspellen hoeveel extra meldingen Lareb bij een volgende

6/10

This implies that the volume of reports has exceeded LAREB's initial projections by a factor of approximately 16 (235,239 / 15,000 = 15.68) for all adverse reactions and by a factor of roughly 10.5 (6,223 / 600 = 10.37) for serious adverse events. It is perplexing that the Marketing Authorisation Holder (MEB) did not take the step of suspending the marketing authorizations much earlier, given these substantial discrepancies.

Moreover, it's worth noting that the package leaflet of Pfizer's Comirnaty explicitly mentions side effects such as myocarditis and pericarditis, with this term appearing 20 times. These adverse effects pose a particular risk for boys and young men. Additionally, there have been reported cases of

[17] https://voorwaarheid.nl/wp-content/uploads/2022/03/2022-03-09-Tuchtklacht-Pels-Rijcken-bijlage-2-WOB-Draaiboek-LAREB-Veiligheidsbewaking-Corona-pandemie-mei-2020.pdf

fatalities.

Myocarditis and pericarditis

There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The package leaflet for Moderna's Spikevax similarly highlights the risk of myocarditis and pericarditis, with this term appearing 12 times. Moreover, there have also been documented cases of fatalities,

1 van 12 gevonden Bevat myocarditis and p

Hypersensitivity and anaphylaxis

Anaphylaxis has been reported in individuals who have received Spikevax. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. Subsequent doses of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Spikevax.

Myocarditis and pericarditis

There is an increased risk for myocarditis and pericarditis following vaccination with Spikevax.

These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have been observed more often in younger males, and more often after the second dose compared to the first dose (see section 4.8).

Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

b. Lack of therapeutic efficacy and unacceptable risks of side effects

A fundamental requirement for a vaccine is to stimulate long-term immunity.[18] If a vaccine only offers protection for less than a year, it falls short of this crucial criterion. Immunity entails establishing a durable defense, which is not achieved in such cases.

c) Lack of declared qualitative and quantitative properties.

In terms of quality, it is important to emphasize that the vaccines do not effectively prevent transmission, rendering the slogan "You're doing it for someone else" inapplicable. Consequently, these drugs are prescribed off-label, necessitating informed consent that explicitly outlines the risk of mortality and the fact that the medication is not approved for transmission prevention.

[18] https://www.cdc.gov/vaccines/vac-gen/imz-basics.htm#diseases

In quantitative terms, it should be noted that the vaccines have not met the claim that vaccination would render 70% to 95% of individuals immune to infection.[19]

c. The documents submitted are incorrect
Due to irregularities and illegalities in altering the categorization of medicines, drugs that have undergone inadequate safety research have erroneously been introduced to the market. Changes in the rolling review and conditional marketing authorization procedures, as well as modifications to the definitions of vaccines and immunity, have rendered the criteria inadequate. Furthermore, significant irregularities have been identified in clinical trial data, and these concerns have been reported multiple times in the British Medical Journal (BMJ).[20]

d. Inserts do not meet requirements
The Summary of Product Characterisations (SMPCs also called leaflets for *professionals*) submitted by Pfizer and Moderna are so voluminous that they have become de facto illegible for both doctors and citizens making informed consent impossible.

In addition, it is not allowed to create 1 package leaflet for different products. The XBB.15 boosters qualify as a new medicine, for which a separate leaflet should therefore be designed. The pharmacist cannot expect the doctor and the patient to figure out for themselves which part of such extensive SMPCs (package leaflets), namely 574 pages or 224 pages is about the XBB.15 booster, as shown below.

SMPC Pfizer (574 pages)[21]
SMPC Moderna (224 pages)[22]

The information must be clear and also easily accessible. It is not permissible to lump everything together in the proverbial "big heap", even if the same excipients are used. A separate leaflet should be prepared for each variation. After all, even a small change in sequence can have major consequences. (such as thalidomide where the stereoisomer is teratogenic)

The current leaflets list the variants interchangeably. This is insufficiently specific and therefore not permitted under medical law and medical ethics.

d. There was a breach of good manufacturing practices
Emails sent within the EMA show that there were 3 problems shortly before authorisation. These problems were mainly related to good manufacturing practices.

Wathion Noel
Mon 11/16/2020 12:42 PM
Inbox
Time for decision-making at EU; tomorrow phone call with Olga et al to prepare for EU Exe SG on Wednesday.
Wednesday EU Exe SG with HoAs.
Thursday TC with Commissioner.
The feasibility to "adapt" the CMA to these extraordinary circumstances will be key for determining the approach.
Classified as internal/staff & contractors by the European Medicines Agency

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[19] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9115787/
[20] https://www.bmj.com/content/375/bmj.n2635
[21] https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_nl.pd
[22] https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_nl.pdf

This email argues that the ability to amend the terms of a conditional marketing authorisation is important to the approach.[23]

Nolte Alexis

Mon 23/11/2020 10:48

Sent Items

To:

Korakianiti Evdokia;

Evdokia,

One way to understand how the lower mRNA level in the finished product translates to efficacy would be to measure whether it affects significantly levels of protein expression. It could be that the level of antigenic protein expressed is not significantly affected. However, I don't know whether there is a test that would allow to predict impact on efficacy without clinical trial for comparability.

Alexis

Classified as internal/staff & contractors by the European Medicines Agency

This e-mail states that the lower amount of intact mRNA in the *finished* product might translate into lesser efficacy, thus making the 95% claim underlying the media statements a priori misleading.[24]

Boone Hilde

ma 23/11/2020 14:26

Dear Marco & Irene,

In the EC table, CHMP opinion is presented for 21 December, whereas this morning 23rd was mentioned as per current timetable, I understand.

But, indeed we agreed trying to bring Opinion forward by a few days eg to 21 or even 18 Dec.

So, what response should we give back to EC now:

Current EMA planning is 23 Dec for Opinion, but we are looking into bringing adoption forward?

Or

Do we already say that 21 Dec for Opinion, as listed in the EC table, is correct, but that we are looking into bringing adoption forward even more?

I take it that the Eudralink TT request that we just received, replaces Olga's question below (as it is in essence the same).

Best, Hilde

Classified as internal/staff & contractors by the European Medicines Agency

In this email, it is clear that rather than being guided by thorough research to arrive at an opinion, the EMA is interfering in the substantive process and indicating that approval should be given sooner. This did happen, the Conditional Marketing Authorisation was awarded to Pfizer on 21 December 2020.[25]

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[23] https://voorwaarheid.nl/wp-content/uploads/2022/12/E-mail-4.png
[24] https://voorwaarheid.nl/wp-content/uploads/2022/12/E-mail-7.png
[25] https://voorwaarheid.nl/wp-content/uploads/2022/12/E-mail-14.png

Conclusions: a number of major concerns remain that impact the benefit/risk of the vaccine (efficacy/safety) most notably the comparability issue around % mRNA integrity. These concerns are shared by most member states. **An approval by the end of the year could potentially be possible, if these concerns + GMP will be resolved**. Any remaining Quality issues will need to be considered in the context of overall B/R (& could potentially be addressed via specific obligations/Annex II conditions/recommendations).

The BWP report reflecting these conclusions is undergoing written adoption today.

With thanks to Ton, Brian and Claudio,

Kind regards,

Veronika

Veronika Jekerle, PhD

Head of Pharmaceutical Quality Office

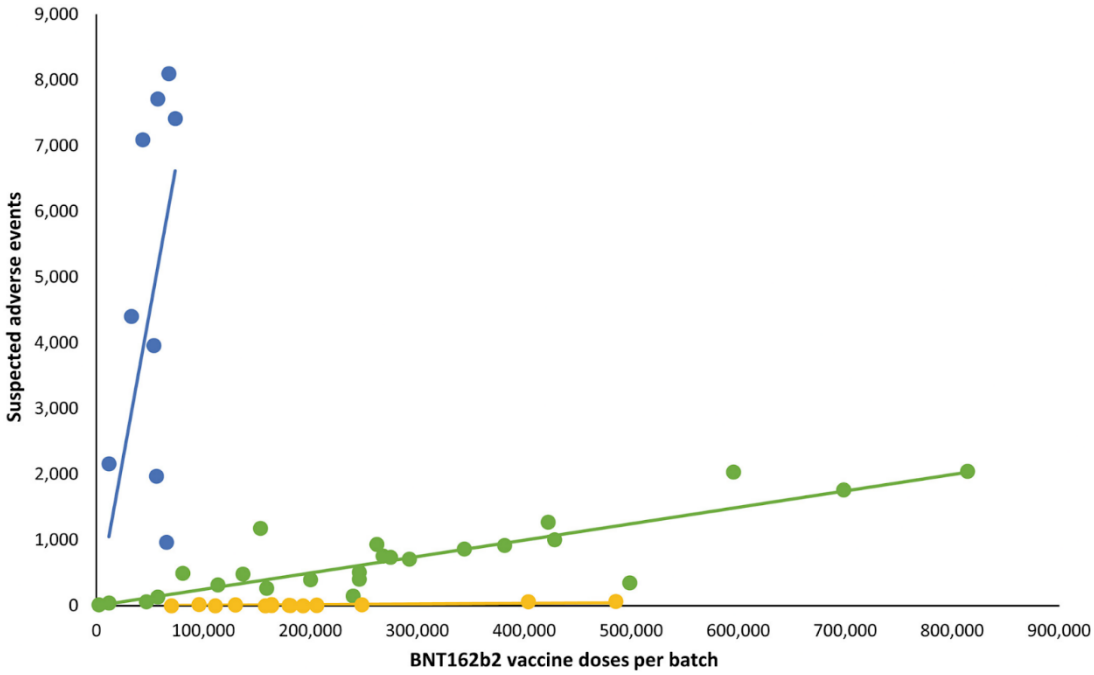
Quality and Safety of Medicines

Office: 09-N-02

Extension: 8438

On 24 November 2020, there was still talk of 3 Major Objections;
1. The mRNA integrity depends on Good Manufacturing Practices (GMP). A problem was identified with mRNA integrity.
2. The *clinical batches* used for the *clinical trials* differed significantly from the *commercial batches*.
3. Finally, there was also a lot of difference between different production facilities.[26]

The batch homogeneity did not appear to be in order. That this in turn affected the benefit/risk ratio, aka efficacy/safety ratio was shown in the publication: Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine, Maniche et al, 30 March 2023.[27]
In this publication, reports of adverse events depend on batch number. This correlation is significant. 4% of doses account for 70% of reports.



[26] https://voorwaarheid.nl/wp-content/uploads/2022/12/E-mail-9.png
[27] https://onlinelibrary.wiley.com/doi/10.1111/eci.13998

A drug so diverse in action cannot be authorised, if only because of the impossibility of informed consent. In addition, as a precautionary principle, the highest category of side effects must be assumed. This makes an effectiveness/safety trade-off negative for each specific target group.

Interim conclusion**:** As many as 6 out of 10 categories have not been met, which is why you should proceed to immediate suspension.

Union licence for Pfizer and Moderna

The Conditional Marketing Authorisation for Pfizer and Moderna awarded on 21 December 2020 and 6 January 2021 do not meet the requirements as Regulation 2019/5/EU[28] & Regulation 2020/1043/EU[29] & Regulation 2021/756/EU[30] do not meet the framework laid down:

- On environmental risk assessment and reporting in Regulation2001/18/EC[31] & Directive 2009/41/EC[32]
- On safety for medicinal products laid down in Directive 2001/83/EC[33] & 2003/63/EC & 2007/1394/EC[34]
- Concerning the granting of a union licence laid down in Regulation 2004/726/EC & Regulation 2008/1234/EC[35]

The changes in Regulation 2019/5/EU should not be used to go outside the framework of existing classification and categorisation, only clarification is allowed, no categories can be added that conflict with the current system, full legislation is needed for that.[36]

The temporary suspension of the environmental risk assessment and reporting (2020/1043) appears to be null and void with this (see chapter 3 of the report Resilient Biotechnology Policy dated 11 October 2022 by COGEM published on 16 December 2022.[37] Particular reference is made to pages 36-38 of the report.

The changes in Regulation 2021/756/EU were done AFTER the first Conditional Marketing Authorisation grant. Article 19 of Regulation 2008/1234 clearly states that follow-up licences should be assessed according to the criteria of the first licence.[38]

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[28] https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:32019R0005&qid=1695804802708
[29] https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:32020R1043
[30] https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:32021R0756
[31] https://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0009.02/DOC_1&format=PDF
[32] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:125:0075:0097:EN:PDF
[33] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083
[34] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32007R1394
[35] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1234-20130804
[36] https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:32019R0005&qid=1695804802708
[37] https://cogem.net/app/uploads/2022/12/CGM-2022-05-Veerkrachtig-biotechnologiebeleid.pdf
[38] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1234-20130804

CHAPTER IV

SECTION 1

Special procedures

Article 19

Extensions of marketing authorisations

1. An application for an extension of a marketing authorisation shall be evaluated in accordance with the same procedure as for the initial marketing authorisation to which it relates.

2. An extension shall either be granted a marketing authorisation in accordance with the same procedure as for the granting of the initial marketing authorisation to which it relates or be included in that marketing authorisation.

In addition, the addition of 'codes/sequences' in Regulation 2021/756/EU conflicts with the classification and categorisation of Directive 2001/83/EC[39] & Directive 2003/63/EC[40] & Regulation 2007/1394.[41]

Regulation 2009/120/EC making change to Annex part IV namely art 2.1 *"Gene therapy medicinal products shall not include vaccines against infectious diseases"* offers no relief, the last rule should be seen as mutually exclusive. After all, vaccine is already defined by the regulations that appeared before.[42]

A vaccine must induce immunity appears from Article 1(4) Directive 2001/83/EC:[43]

4. *Immunological medicinal product:*

Any medicinal product consisting of vaccines, toxins, serums or allergen products:

(a) vaccines, toxins and serums shall cover in particular:

(i) agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine;

(ii) agents used to diagnose the state of immunity, including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin;

(iii) agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin;

(b) 'allergen product' shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent.

Article 1.4 (immunological medicine) of this Regulation says "immune response" , but immunity. These are two completely different things. Immunity is a specific immune response where infection is prevented in the future, in the current injections there is no evidence of that.

[39] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083
[40] https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:32003L0063
[41] https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:32007R1394
[42] https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:32009L0120&qid=1696174935335
[43] https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:32001L0083

In addition, a vaccine must contain an antigen; this antigen requires its own registration in the Vaccine Antigen Master File (VAMF) laid down in Directive 2003/63/EC.[44] The reason for this method is that homogeneity and quality and active dose can be determined per treatment. This is not the case with coding sequences.

The recommendations for categorisation and interpretation of the law is reflected in the EMA's *guidelines*.

Reflection paper on classification of advanced therapy medicinal products 2015
According to this paper, and especially paragraph 2.3.3, mRNA is considered an example of gene therapy.[45]

Reflection paper on criteria to be considered for the 6 evaluation of new active substance (NAS) status of 7 biological substances 2023
According to this paper and especially 5.8 which states that any significant change in the sequence of mRNA requires a new application.[46]

Thereby, it must be established that parts of Regulation 2020/1043/EU[47] and Regulation 2021/756/EU[48] are contrary to the classification system and the security system, as argued in the COGEM report, they are thus contrary to Articles 141 and 168 TFEU.

In addition, 2019/5 was used in violation of Article 290(1) of the Treaty on the Functioning of the European Union ("TFEU"):

> *"A legislative act may delegate to the Commission the power to adopt non-legislative acts of general application to supplement or amend certain non-essential elements of the legislative act."*

It is clearly stated that delegation of powers is not about legislative acts. If classification and categorisation acts and provision are in conflict with existing classification and categories it is WELL legislation, thus all such acts are null and void. In addition, the same line can be followed as the changes lead to a greater risk to public health (see Article 168 TFEU).

The issues are discussed in detail in this publication by Helene Banoun, 9 June 2023, International Journal of Molecular Sciences.[49]

Conclusion
Your role as a medicines agency carries an inherent commitment to the principles of good administration and good medical practice. Failing to suspend the marketing authorizations in question would not only be incongruent with these principles but may also implicate human rights considerations, given the gravity of the issues at hand.

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[44] https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:32003L0063
[45] https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf
[46] https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-criteria-be-considered-evaluation-new-active-substance-nas-status-biological_en.pdf
[47] https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:32020R1043
[48] https://eur-lex.europa.eu/legal-content/NL/TXT/PDF/?uri=CELEX:32021R0756
[49] https://www.mdpi.com/1422-0067/24/13/10514

The stakes involved encompass not only the well-being of our citizens but also the allocation of taxpayers' funds.

Therefore, it is imperative that immediate action is taken to suspend the following marketing authorizations:
- Conditional Marketing Authorisation Pfizer (Comirnaty) dated 21 December 2020.;[50]
- Conditional Marketing Authorisation Moderna (Spikevax) dated 6 January 2021[51]
- Renewal of Marketing Authorisation Pfizer (Comirnaty-tozinameran) dated 31 August 2023;[52]
- Renewal Marketing Authorisation Moderna (Spikevax-elasomeran) dated 15 September 2023.[53]

We kindly request an acknowledgment of receipt and anticipate a comprehensive response to this request at your earliest convenience.

Sincerely,

Marcel de Graaff (Member of the European Parliament)
Gilbert Collard (Member of the European Parliament)
Francesca Donato (Member of the European Parliament)
Joachim Kuhs (Member of the European Parliament)
Mislav Kolakušić (Member of the European Parliament)
Virginie Joron (Member of the European Parliament)
Ivan Vilibor Sinčić (Member of the European Parliament)
Bernhard Zimniok (Member of the European Parliament)

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[50] https://ec.europa.eu/health/documents/community-register/2020/20201221150522 /dec_150522_en.pdf
[51] https://ec.europa.eu/health/documents/community-register/ 2021/20210106150575/ dec_150575_en.pdf
[52] https://ec.europa.eu/health/documents/community-register/2023/202308311 60389/dec_160389 _en.pdf
[53] https://ec.europa.eu/health/documents/community-register/2023/2023091 5160561/dec_160561_en.pdf

Frances R. Oleen, #17433
Deputy Attorney General
Kaley Schrader, #27700
Assistant Attorney General
Office of the Attorney General
Public Protection Division
120 SW 10th Ave., 2nd Floor
Topeka, Kansas 66612-1597
Tel: 785-296-3751
Fax: 785-291-3699
kaley.schrader@ag.ks.gov

IN THE DISTRICT COURT OF THOMAS COUNTY, KANSAS

STATE OF KANSAS, *ex rel.*	)
KRIS W. KOBACH, Attorney General,	)
	)
Plaintiff,	)
	)
v.	)
	)
PFIZER INC.,	)
	)
Defendant.	)
	)

Pursuant to K.S.A. Chapter 60

PETITION

COMES NOW the Plaintiff, State of Kansas, *ex rel.* Kris W. Kobach, Attorney General, by and through Assistant Attorney General Kaley Schrader, and for its cause of action against Defendant, alleges and states as follows:

NATURE OF THE ACTION

1. Pfizer misled the public that it had a "safe and effective" COVID-19 vaccine.

2. Pfizer said its COVID-19 vaccine was safe even though it knew its COVID-19 vaccine was connected to serious adverse events, including myocarditis and pericarditis, failed pregnancies, and deaths. Pfizer concealed this critical safety information from the public.

3. Pfizer said its COVID-19 vaccine was effective even though it knew its COVID-19 vaccine waned over time and did not protect against COVID-19 variants. Pfizer concealed this critical effectiveness information from the public.

4. Pfizer said its COVID-19 vaccine would prevent transmission of COVID-19 even though it knew it never studied the effect of its vaccine on transmission of COVID-19.

5. To keep the public from learning the truth, Pfizer worked to censor speech on social media that questioned Pfizer's claims about its COVID-19 vaccine.

6. Pfizer's misrepresentations of a "safe and effective" vaccine resulted in record company revenue of approximately $75 billion from COVID-19 vaccine sales in just two years.

7. Pfizer's actions and statements relating to its COVID-19 vaccine violated previous consent judgments with the State of Kansas.

8. Pfizer's actions and statements relating to its COVID-19 vaccine violated the Kansas Consumer Protection Act, K.S.A. 50-623 *et seq.*, regardless of whether any individual consumer ultimately received Pfizer's COVID-19 vaccine.

9. Pfizer must be held accountable for falsely representing the benefits of its COVID-19 vaccine while concealing and suppressing the truth about its vaccine's safety risks, waning effectiveness, and inability to prevent transmission.

PARTIES

10. Plaintiff Kris W. Kobach is the duly elected, qualified, and acting Attorney General for the State of Kansas.

11. The Attorney General has standing to bring this action in the name of the State of Kansas by statute. K.S.A. 50-628(a)(1), 50-632(a); *see also* K.S.A. 75-702(a).

12. The Attorney General has standing to bring this action under the common law of this State on behalf of all Kansans.

13. The Attorney General has standing to bring this action under consent judgments between the State of Kansas and Pfizer.

14. Defendant Pfizer Inc. ("Pfizer") is a publicly traded corporation organized in the State of Delaware and with a principal place of business in New York, New York. Pfizer has been registered to do business in Kansas since June 8, 1993.

15. Defendant Pfizer may be served through its resident agent CT Corporation System, 112 SW 7th Street, Suite 3C, Topeka, Kansas, 66603.

16. Pfizer's acts include acts by Pfizer and acts by Pfizer's officers, directors, agents, or employees on Pfizer's behalf and under its authority.

17. Actions or statements by Pfizer Chairman and CEO Dr. Albert Bourla and Pfizer Board Member Dr. Scott Gottlieb are attributable to Pfizer.

JURISDICTION AND VENUE

18. This Court has jurisdiction over this case pursuant to K.S.A. 20-301 and K.S.A. 50-638(a).

19. Pfizer is registered to do business in Kansas as a foreign corporation, and the cause of action arose in Kansas from Pfizer conducting business in Kansas. Therefore, Pfizer is subject to personal jurisdiction in Kansas pursuant to K.S.A. 17-7307(c).

20. Pfizer is also subject to personal jurisdiction in Kansas pursuant to K.S.A. 60-308(b)(1)(A) because Pfizer transacts business in Kansas.

21. Venue is proper in this county under K.S.A. 50-638(b). Pfizer's actions and practices that violated the Kansas Consumer Protection Act reached consumers in Thomas County.

ALLEGATIONS COMMON TO ALL COUNTS

22. Plaintiff incorporates all preceding paragraphs by reference.

23. At all times relevant hereto, and in the ordinary course of business, Pfizer acted as a "supplier," as that term is defined by K.S.A. 50-624(l).

24. At all times relevant hereto, and in the ordinary course of business, Pfizer made, caused to be made, or solicited, "consumer transactions," as that term is defined by K.S.A. 50-624(c).

25. Upon information and belief, because of the high public interest in Pfizer's COVID-19 vaccine, Pfizer's actions and statements circulated widely throughout Kansas.

26. Statements on Pfizer's website and social media have made misrepresentations to Kansans from the day they were posted continuing to the present.

27. Pfizer's misrepresentations about its COVID-19 vaccine violated the Kansas Consumer Protection Act and Pfizer's consent judgments with Kansas each time Pfizer made them to a Kansas consumer, regardless of whether an individual consumer decided to receive or forgo Pfizer's COVID-19 vaccine.

28. Millions of Kansans heard Pfizer's misrepresentations about its COVID-19 vaccine. For example, Pfizer administered 3,355,518 Pfizer vaccine doses in Kansas as of February 7, 2024. This accounted for more than 60% of all vaccine doses in Kansas. Kansas Department of Health and Environment, *Data*.[1]

29. In May 2021, Pfizer advertised to Kansans on Facebook about its "life-saving vaccines" and its "cures." Upon information and belief, Pfizer intended for Kansans to think of

[1] *Available at* https://www.coronavirus.kdheks.gov/317/Data. Since this data was collected, the Kansas Department of Health and Environment no longer publicly reports vaccine doses by manufacturer.

its COVID-19 vaccine when it discussed "life-saving vaccines" and "cures." Pfizer ran three different ads between May 4, 2021 and June 1, 2021 that received 165,000 to 190,000 impressions [views] in Kansas. Meta Ad Library, Summary Data for Ads 2974674432763576,[2] 1144557279322749,[3] and 468595664399043.[4]

30. Pfizer took advantage of Kansans' fear of COVID-19 and desire for safety by offering a "safe and effective" COVID-19 vaccine, while concealing, suppressing, and omitting material information that undermined its safety and effectiveness claims.

I. Pfizer's Big Bet on Its COVID-19 Vaccine

31. COVID-19 is caused by the virus SARS-CoV-2 and originated in Wuhan, China.

32. In 2020, Pfizer raced to develop a COVID-19 vaccine.

33. Unlike the other companies involved in the race for a vaccine, Pfizer did not join Operation Warp Speed and declined its vaccine development funding. *Transcript, Pfizer CEO Dr. Albert Bourla on 'Face the Nation*,'" CBS News, Sept. 13, 2020;[5] Carolyn Y. Johnson, *Pfizer's coronavirus vaccine is more than 90 percent effective in first analysis, company reports*, THE WASHINGTON POST (Nov. 9, 2020).[6]

34. Pfizer distanced itself from Operation Warp Speed when it announced the results of its COVID-19 vaccine trials: "We were never part of the Warp Speed," proclaimed Pfizer's senior vice president and head of vaccine research and development. Philip Bump, *No, Pfizer's*

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[2] *Available at* https://www.facebook.com/ads/library/?id=2974674432763576.
[3] *Available at* https://www.facebook.com/ads/library/?id=1144557279322749.
[4] *Available at* https://www.facebook.com/ads/library/?id=468595664399043.
[5] *Available at* https://www.cbsnews.com/news/transcript-pfizer-ceo-dr-albert-bourla-on-face-the-nation-september-13-2020/.
[6] *Available at* https://www.washingtonpost.com/health/2020/11/09/pfizer-coronavirus-vaccine-effective/.

apparent vaccine success is not a function of Trump's 'Operation Warp Speed,' THE WASHINGTON POST (Nov. 9, 2020).[7]

35. Pfizer's Chairman and CEO Dr. Bourla, a veterinarian by training, reported that Pfizer declined government funding in order to "liberate" Pfizer's scientists from government oversight of its vaccine development: "But the reason why I did it was because I wanted to liberate our scientists from any bureaucracy. **When you get money from someone that always comes with strings. They want to see how we are going to progress, what type of moves you are going to do. They want reports. I didn't want to have any of that**." *Transcript, Pfizer CEO Dr. Albert Bourla on 'Face the Nation*,'" CBS NEWS, Sept. 13, 2020 (emphasis added).[8]

36. Because Pfizer did not accept government funding, "[t]he government had limited visibility into what was happening at Pfizer, …" Sydney Lupkin, *The U.S. Paid Billions To Get Enough COVID Vaccines Last Fall. What Went Wrong?* NPR (Aug. 25, 2021).[9]

37. "Pfizer worked 'at arm's length' compared with the other companies in Operation Warp Speed," the scientific lead of Operation Warp Speed recounted. *Id.*

38. Pfizer's independence from Operation Warp Speed allowed it to demand a "tailor-made contract" that let Pfizer "retain almost all of its intellectual property rights and forgo the taxpayer protection clauses found in most government contracts that fund inventions." *Id.*; *see also* Statement of Work for COVID-19 Pandemic-Large Scale Vaccine Manufacturing Demonstration, July 21, 2020 ("Pfizer Statement of Work"), ¶¶ 7.1, 7.2 (PDF pp. 19-20).[10]

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[7] *Available at* https://www.washingtonpost.com/politics/2020/11/09/no-pfizers-apparent-vaccine-success-is-not-function-trumps-operation-warp-speed/.
[8] *Available at* https://www.cbsnews.com/news/transcript-pfizer-ceo-dr-albert-bourla-on-face-the-nation-september-13-2020/.
[9] *Available at* https://www.npr.org/sections/health-shots/2021/08/25/1029715721/pfizer-vaccine-operation-warp-speed-delay.
[10] *Available at* https://www.hhs.gov/sites/default/files/pfizer-inc-covid-19-vaccine-contract.pdf.

39. By self-funding, Pfizer was betting big that its vaccine development would succeed. "[I]f it fails, it goes to our pocket," warned Pfizer Chairman and CEO Dr. Bourla. *Transcript, Pfizer CEO Dr. Albert Bourla on 'Face the Nation*,'" CBS NEWS, Sept. 13, 2020.[11]

40. By September 2020, Pfizer had invested at least $1.5 billion for COVID vaccine development. Losing this money by failing to develop an approved vaccine would be "painful," admitted Pfizer Chairman and CEO Dr. Bourla. *Id.*

41. Based on Pfizer's public statements, Pfizer would lose $1.5 billion to $2 billion if government regulators did not approve its COVID-19 vaccine. *See id.*; Pfizer 2021 Annual Report, *Expanding COVID-19 Manufacturing Efforts to Increase Global Vaccine Access*.[12]

42. Pfizer's contract with the federal government—in which Pfizer would deliver 100 million doses in exchange for $1.95 billion—required Pfizer to obtain approval of its COVID-19 vaccine. *Pfizer and BioNTech Announce an Agreement with U.S. Government for up to 600 Million Doses of mRNA-based Vaccine Candidate Against SARS-CoV-2*, July 22, 2020.[13]

43. Pfizer doubled down on its bet that its vaccine would receive federal government approval by producing a "few million" vaccine doses before it received the efficacy or safety data from its vaccine trial or government approval. *Pfizer CEO says he would've released vaccine data before election if possible*, AXIOS, Nov. 9, 2020.[14]

44. Pfizer's CEO had a personal financial interest in Pfizer succeeding.

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[11] *Available at* https://www.cbsnews.com/news/transcript-pfizer-ceo-dr-albert-bourla-on-face-the-nation-september-13-2020/.
[12] *Available at* https://www.pfizer.com/sites/default/files/investors/financial_reports/annual_reports/2021/story/expanding-covid-manufacturing-efforts/.
[13] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-agreement-us-government-600.
[14] *Available at* https://www.axios.com/2020/11/09/pfizer-ceo-says-he-wouldve-released-vaccine-data-before-election-if-possible.

45. In August 2020, Pfizer Chairman and CEO Dr. Bourla implemented a plan to sell some of his Pfizer stock if it reached a pre-determined price just one day before Pfizer issued a press release "featuring 'additional Phase 1 safety and immunogenicity data' and confirming that Pfizer and its German partner, BioNTech, were 'on track to seek regulatory review' for its vaccine candidate by October. The financial news channels Fox Business, CNBC, and Bloomberg all covered the August news, with CNBC noting that [Pfizer's] stock appeared to be 'moving sharply higher today on an optimistic vaccine timeline.'" Tom Dreisbach, *Pfizer CEO Sold Millions In Stock After Coronavirus Vaccine News, Raising Questions*, NPR, Nov. 11, 2020.[15]

46. Pfizer Chairman and CEO Dr. Bourla's stock reached the pre-determined price and sold on November 9, 2020, "the same day Pfizer announced that its experimental coronavirus vaccine candidate was found to be more than 90% effective. The company's stock soared on the news." *Id.*

47. Pfizer Chairman and CEO Dr. Bourla made $5.6 million from his November 9, 2020 Pfizer stock sale. *Id.*

48. An insider-trading expert called the sequence of events involving Pfizer Chairman and CEO Dr. Bourla's stock sale "very suspicious," "wholly inappropriate," and "troubling." *Id.*

49. Pfizer had billions of incentives to do whatever it took to ensure that its COVID-19 vaccine received the necessary government approval.

50. Pfizer received emergency use authorization for its COVID-19 vaccine in individuals 16 years of age and older on December 11, 2020. FDA, *FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine*,

[15] *Available at* https://www.npr.org/2020/11/11/933957580/pfizer-ceo-sold-millions-in-stock-after-coronavirus-vaccine-news-raising-questio.

Dec. 11, 2020.[16] Emergency Use Authorizations "can be used by the FDA during public health emergencies to provide access to medical products that may be effective in preventing, diagnosing, or treating a disease, provided that the FDA determines that the known and potential benefits of a product, when used to prevent, diagnose, or treat the disease, outweigh the known and potential risks of the product." FDA, *FDA Approves First COVID-19 Vaccine*, Aug. 23, 2021.[17]

51. Pfizer received FDA approval for its COVID-19 vaccine in individuals 16 years of age and older on August 23, 2021. *Id.*

52. From 2021 to 2023, Pfizer received emergency use authorizations for its COVID-19 vaccine in children from six months to 15 years of age, as well as for booster doses. *See, e.g.*, U.S. Dep't of Health and Human Servs., *COVID-19 Vaccine Milestones*.[18]

II. Pfizer's COVID-19 Vaccine and Transparency

A. Pfizer's representations about transparency

53. Pfizer repeatedly assured Kansans that it provided transparency on its data.

54. On December 14, 2020, the day Americans began receiving Pfizer's COVID-19 vaccine, Pfizer Chairman and CEO Dr. Bourla said, "This is a vaccine that was developed without cutting corners from a company with 171 years of credentials. This is a vaccine that was developed in the spotlight in the daylight, with all the data being put in servers." *CNBC Transcript: Pfizer Chairman and CEO Albert Bourla Speaks with CNBC's 'Squawk Box' Today*, CNBC (Dec. 14, 2020).[19]

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[16] *Available at* https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19.
[17] *Available at* https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine.
[18] *Available at* https://www.hhs.gov/coronavirus/covid-19-vaccines/index.html.
[19] *Available at* https://www.cnbc.com/2020/12/14/cnbc-transcript-pfizer-chairman-and-ceo-albert-bourla-speaks-with-cnbcs-squawk-box-today.html.

55. On September 16, 2021, Pfizer Chairman and CEO Dr. Bourla said, "Since the start of this pandemic, Pfizer and BioNTech have pledged to follow the science and keep people informed about our progress to help bring an end to this global health crisis. We have stayed true to our commitment of full transparency without selectively cherry-picking data." *Continuing to Follow the Science: An Open Letter from Pfizer Chairman and CEO Dr. Albert Bourla*, Pfizer, Sept. 16, 2021.[20]

56. Contrary to its representations, Pfizer has willfully concealed, suppressed, and omitted safety and efficacy data relating to its COVID-19 vaccine.

B. Pfizer used confidentiality agreements to conceal critical data relating to the safety and effectiveness of its COVID-19 vaccine.

57. Pfizer has kept data hidden through confidentiality agreements with governments around the world.

58. Pfizer's contract required the United States government to keep Pfizer's confidential information secret for 10 years. Higher protections applied to Pfizer's trade secret information, which the government promised to keep "in confidence in perpetuity." Pfizer Statement of Work, ¶ 11.10 (PDF p. 25).[21]

59. Pfizer effectively had a veto over the federal government's communications because the parties agreed that they would not make any public announcement relating to the COVID-19 vaccine contract or "the transactions contemplated by it" without the prior written consent of the other. *Id.* at ¶ 11.11 (PDF p. 25).

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[20] *Available at* https://www.pfizer.com/news/announcements/continuing-follow-science-open-letter-pfizer-chairman-and-ceo-dr-albert-bourla.
[21] *Available at* https://www.hhs.gov/sites/default/files/pfizer-inc-covid-19-vaccine-contract.pdf.

60. Conversely, Pfizer had exclusive control over its own communications through "the right, but not the obligation, to prepare and submit scientific publications and release information to the public about its COVID-19 development program, without the Government's consent or involvement." *Id.*

61. Upon information and belief, Pfizer used its confidentiality agreements with the United States government and others to conceal, suppress, and omit material facts relating to Pfizer's COVID-19 vaccine, including the safety and efficacy of the vaccine.

C. Pfizer used an extended study timeline to conceal critical data relating to the safety and effectiveness of its COVID-19 vaccine.

62. Pfizer also kept data hidden through a study timeline that Pfizer repeatedly delayed.

63. Pfizer planned to provide researchers with access to patient-level data and full clinical study reports 24 months after study completion. Protocol C4591001, "A Phase 1/2, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Adults," ("Apr. 2020 Protocol"), Pfizer, Apr. 15, 2020, 104 (PDF p. 106), ¶ 10.1.4.[22]

64. Pfizer initially estimated that it would complete the study by January 27, 2023, but that estimated date fell back to February 2024 because of a late vaccination of a single study participant (out of 44,000 participants). Jennifer Block, *COVID-19: Researchers face wait for patient level data from Pfizer and Moderna vaccine trials*, BRITISH MEDICAL JOURNAL, July 12, 2022;[23] *see also* Pfizer's Clinical Study Records.[24]

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[22] *Available at* https://www.nejm.org/doi/suppl/10.1056/NEJMoa2027906/suppl_file/nejmoa2027906_protocol.pdf.
[23] *Available at* https://www.bmj.com/content/378/bmj.o1731.
[24] *Available at* https://www.clinicaltrials.gov/study/NCT04368728?term=C4591001&rank=2&tab=history&a=.

65. Scientists were outraged that they still could not review Pfizer's COVID-19 study data. "Pfizer's pivotal COVID vaccine trial was funded by the company and designed, run, analysed, and authored by Pfizer employees. The company and the contract research organisations that carried out the trial hold all the data." *COVID-19 vaccines and treatments: we must have raw data, now*, British Medical Journal, 2022:376 (Jan. 19, 2022).[25]

66. Pfizer's control of the data allowed the company to selectively publish results for which the underlying data could not be independently evaluated. *See id.*

67. As the British Medical Journal editorialized in January 2022:

> Pharmaceutical companies are reaping vast profits without adequate independent scrutiny of their scientific claims. The purpose of regulators is not to dance to the tune of rich global corporations and enrich them further; it is to protect the health of their populations. We need complete data transparency for all studies, we need it in the public interest, and we need it now.

Id.

68. Perhaps due to a production ruling in a Freedom of Information Act ("FOIA") lawsuit against the FDA, *see infra*, and the increased frustration expressed by scientists, Pfizer finally completed its study on February 10, 2023.

69. Pfizer today says it will make data from vaccine trials approved in the United States available 18 months after the primary study completion date. Pfizer, *Data Access Requests*.[26]

70. Upon information and belief, Pfizer has still not made its complete study data available to researchers.

D. Pfizer used FOIA denial and delay to conceal critical data relating to the safety and effectiveness of its COVID-19 vaccine.

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[25] *Available at* https://www.bmj.com/content/376/bmj.o102.
[26] *Available at* https://www.pfizer.com/science/clinical-trials/trial-data-and-results/data-requests.

71. The Food and Drug Administration's refusal to immediately produce safety and effectiveness data for Pfizer's COVID-19 vaccine kept Pfizer's data hidden from the public.

72. The Food and Drug Administration granted full approval for Pfizer's COVID-19 vaccine in adults on August 23, 2021. *Pfizer-BioNTech COVID-19 Vaccine COMIRNATY® Receives Full U.S. FDA Approval for Individuals 16 Years and Older*, Aug. 23, 2021.[27]

73. Full approval of Pfizer's COVID-19 vaccine should have made Pfizer's "safety and effectiveness data and information, … adverse reaction reports, product experience reports, [and] consumer complaints … immediately available for public disclosure." *See* 21 C.F.R. 601.51(e).

74. Safety and effectiveness data includes all studies and tests on animals and humans. 21 C.F.R. § 601.51(g).

75. But the FDA did not make the safety and effectiveness data for Pfizer's COVID-19 vaccine immediately available.

76. Because full data was not available, Public Health and Medical Professionals for Transparency in America ("PHMPTA") submitted a FOIA request to the FDA for all data and information for Pfizer's COVID-19 vaccine. *Pub. Health & Med. Pros. for Transparency v. Food & Drug Admin.*, No. 4:21-CV-1058-P, Doc. 1-1 (Aug. 27, 2021 request).

77. Pfizer's contract with the federal government granted Pfizer at least 30 days to review any records the government planned to release and the power to identify documents and information "legally withholdable from release under FOIA." Pfizer Statement of Work, ¶ 7.2 (PDF p. 20).[28]

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[27] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-biontech-covid-19-vaccine-comirnatyr-receives-full.
[28] *Available at* https://www.hhs.gov/sites/default/files/pfizer-inc-covid-19-vaccine-contract.pdf.

78. FOIA does not provide a third-party like Pfizer with rights to review documents before their release or to identify withholdable documents. Pfizer's COVID-19 vaccine contract thus provided Pfizer with rights over government documents not typically possessed by private businesses.

79. The FDA denied expedited processing of PHMPTA's FOIA request and claimed in litigation that it would take 55 years—until 2076—to produce all of the responsive documents. Jenna Greene, *Wait what? FDA wants 55 years to process FOIA request over vaccine data*, REUTERS, Nov. 18, 2021.[29]

80. Upon information and belief, Pfizer and its contractual rights to review documents before their release and to identify withholdable documents influenced the FDA's decision to deny expedited processing of PHMPTA's FOIA request and propose a 55-year production timeline.

81. Upon information and belief, Pfizer thus had a role in keeping its safety and effectiveness data possessed by the FDA hidden from the public.

82. In January 2022, a federal judge rejected the FDA's proposed production of 500 pages per month and ordered the FDA to instead produce 55,000 pages per month. *Pub. Health & Med. Pros. for Transparency v. Food & Drug Admin.*, No. 4:21-CV-1058-P, 2022 WL 90237, at *2 (N.D. Tex. Jan. 6, 2022).

E. Pfizer destroyed the vaccine control group, which will conceal critical data relating to the safety and effectiveness of its COVID-19 vaccine.

83. Finally, Pfizer kept its COVID-19 vaccine's true effects hidden by destroying the control group participating in its vaccine trial.

[29] *Available at* https://www.reuters.com/legal/government/wait-what-fda-wants-55-years-process-foia-request-over-vaccine-data-2021-11-18/.

84. A double-blind study, in which both the study subjects and study investigators do not know which group received the treatment or the placebo, is "the gold standard in modern clinical trials" and is "designed to test a treatment's safety and efficacy." Pfizer, *How the Placebo Effect Can Cloud Clinical Trial Results*.[30]

85. Pfizer promoted that it was conducting a double-blind study on its COVID-19 vaccine "to obtain safety, immune response, and efficacy data needed for regulatory review." Pfizer, *Pfizer and BioNTech Choose Lead mRNA Vaccine Candidate Against COVID-19 and Commence Pivotal Phase 2/3 Global Study*, July 27, 2020;[31] *see also* Apr. 2020 Protocol, *supra*, 30 (PDF p. 32).

86. Pfizer planned to follow COVID-19 vaccine study participants, both vaccine and placebo recipients, for 24 months to monitor the safety and effectiveness of its vaccine. Apr. 2020 Protocol, *supra*, 94-95 (PDF p. 96-97).

87. Once the FDA approved Pfizer's COVID-19 vaccine through an emergency use authorization in December 2020, Pfizer unblinded the study participants and offered vaccine placebo recipients the option to receive the Pfizer COVID-19 vaccine. Stephen J. Thomas et al., *Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine through 6 months*, N. Eng. J. Med., Sept. 15, 2021.[32]

88. Of the 21,921 vaccine trial participants who received the placebo, more than 20,000 placebo participants decided to receive the Pfizer COVID-19 vaccine as of March 13, 2021. BLA Clinical Review Memorandum, Aug. 23, 2021, at 32.[33]

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[30] *Available at* https://www.pfizer.com/news/articles/how_the_placebo_effect_can_cloud_clinical_trial_results.
[31] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate.
[32] *Available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8461570/.
[33] *Available at* https://www.fda.gov/media/152256/download.

89. Taken together, only 1,544 placebo participants had not received the Pfizer COVID-19 vaccine as of March 13, 2021, just 7% of the original placebo group. *See id.*

90. Because Pfizer unblinded the original control group and allowed them to receive Pfizer's COVID-19 vaccine, Pfizer, government regulators, and independent scientists cannot fully compare the safety and efficacy of Pfizer's COVID-19 vaccine against unvaccinated individuals.

91. Pfizer's extensive and aggressive efforts to keep its COVID-19 vaccine information hidden conflict with its public transparency pledges and raise serious questions about what Pfizer is hiding and why it is hiding it.

III. Pfizer's COVID-19 Vaccine and Safety

A. Pfizer's representations about its COVID-19 vaccine and safety

92. In an open letter to the public, Pfizer Chairman and CEO Dr. Bourla dedicated his company to producing a safe vaccine: "The second requirement is to prove that the vaccine is safe. Our internal standards for vaccine safety and those required by regulators are set high. . . . **Safety is, and will remain, our number one priority**, and we will continue monitoring and reporting safety data for all trial participants for two years." *An Open Letter from Pfizer Chairman and CEO Albert Bourla*, Pfizer, Oct. 15, 2020 (emphasis added).[34]

93. After committing to Kansans that safety was Pfizer's number one priority with its COVID-19 vaccine, Pfizer and its employees, directors, and agents repeatedly misrepresented to Kansans that Pfizer's COVID-19 vaccine was safe.

94. On November 9, 2020, Pfizer Chairman and CEO Dr. Bourla said, "We feel very good about the safety" of Pfizer's COVID-19 vaccine and that there were "no safety concerns"

[34] *Available at* https://www.pfizer.com/news/announcements/open-letter-pfizer-chairman-and-ceo-albert-bourla.

reported to Pfizer by a review committee. Tommy Brooksbank, *Pfizer CEO on coronavirus vaccine: 'We feel very good about the safety,'* GOOD MORNING AMERICA, Nov. 9, 2020.[35]

95. On April 1, 2021, Pfizer issued a press release confirming "no serious safety concerns through up to six months following second dose" of the Pfizer COVID-19 vaccine. *Pfizer and BioNTech Confirm High Efficacy and No Serious Safety Concerns Through Up to Six Months Following Second Dose in Updated Topline Analysis of Landmark COVID-19 Vaccine Study*, Pfizer, Apr. 1, 2021.[36]

96. On August 23, 2021, Pfizer Chairman and CEO Dr. Bourla said that the Pfizer vaccine "is effective and safe." Antonio Planas, *'Effective and safe': Pfizer CEO says FDA's full approval should result in more vaccinations*, NBC NEWS, Aug. 23, 2021.[37]

97. On September 16, 2021, Pfizer Chairman and CEO Dr. Bourla said, "We have been very successful in developing an effective and safe vaccine." *Continuing to Follow the Science: An Open Letter from Pfizer Chairman and CEO Dr. Albert Bourla*, Pfizer, Sept. 16, 2021.[38]

98. On September 20, 2021, Pfizer announced in a press release that "[i]n participants 5 to 11 years of age, the vaccine was safe, well tolerated and showed robust neutralizing antibody responses." *Pfizer and BioNTech Announce Positive Topline Results From Pivotal Trial of COVID-19 Vaccine in Children 5 to 11 Years*, Pfizer, Sept. 20, 2021.[39]

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[35] *Available at* https://www.goodmorningamerica.com/news/story/pfizer-ceo-coronavirus-vaccine-feel-good-safety-74105879.
[36] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious.
[37] *Available at* https://www.nbcnews.com/news/us-news/effective-safe-pfizer-ceo-says-fda-s-full-approval-should-n1277478.
[38] *Available at* https://www.pfizer.com/news/announcements/continuing-follow-science-open-letter-pfizer-chairman-and-ceo-dr-albert-bourla.
[39] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-positive-topline-results.

99. On November 22, 2021, Pfizer announced that its COVID-19 vaccine "demonstrated 100% efficacy against COVID-19 in longer-term analysis, with no serious safety concerns identified" in children 12 through 15 years of age. *Follow-Up Data From Phase 3 Trial of Pfizer-BioNTech COVID-19 Vaccine Support Safety and High Efficacy in Adolescents 12 Through 15 Years of Age*, Pfizer, Nov. 22, 2021.[40]

B. Pfizer made unsupported representations and concealed material facts relating to safety of its COVID-19 vaccine.

100. What Pfizer knew about its COVID-19 vaccine demonstrates that Pfizer made unsupported representations and concealed material facts relating to its COVID-19 vaccine.

1. Pfizer's vaccine trials provided limited safety information because Pfizer tested only healthy individuals.

101. Vaccine development normally includes testing on "people with typically varying health statuses and from different demographic groups." FDA, *Vaccine Development – 101* (Dec. 14, 2020) (discussing Phase 2).[41] Indeed, vaccine development includes "trial participants who have characteristics (such as age and physical health) similar to the intended recipients for the vaccine." CDC, *How Vaccines are Developed and Approved for Use* (Mar. 30, 2023).

102. Pfizer only tested its COVID-19 vaccine on healthy individuals. Protocol C4591001, "A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals" ("Sept. 2020 Protocol"), Pfizer, Sept. 8, 2020, 36 (PDF p. 164), ¶ 5.1.2.[42]

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[40] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/follow-data-phase-3-trial-pfizer-biontech-covid-19-vaccine.
[41] Available at https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-development-101.
[42] *Available at* https://www.nejm.org/doi/suppl/10.1056/NEJMoa2027906/suppl_file/nejmoa2027906_protocol.pdf.

103. Pfizer excluded unhealthy individuals from its COVID-19 vaccine trials. *Id.* at 37-38 (PDF pp. 165-66), ¶ 5.2.

104. For example, Pfizer excluded from its COVID-19 vaccine trials any individual who had been diagnosed with COVID-19. *Id.* at 37 (PDF p. 165), ¶ 5.2.5.

105. Pfizer excluded from its COVID-19 vaccine trials any immunocompromised individual. *Id.* at 38 (PDF p. 166), ¶ 5.2.8.

106. Pfizer excluded from its COVID-19 vaccine trials any woman who was pregnant or breastfeeding. *Id.* at 38 (PDF p. 166), ¶ 5.2.11.

107. Pfizer excluded individuals who health officials opined were vulnerable to COVID-19, and who accordingly were likely to be interested in a vaccine for COVID-19.

108. Pfizer's representations that its COVID-19 vaccine did not have any safety concerns failed to disclose the material facts that it had only been tested on healthy individuals.

109. Pfizer did not have data to support representations that its vaccine was safe for the general population, such as in individuals who had been diagnosed with COVID-19, who were immunocompromised, or who were pregnant or breastfeeding.

2. Pfizer failed to disclose limitations of its COVID-19 vaccine trials.

110. When Pfizer announced that the FDA had authorized Pfizer's COVID-19 vaccine for emergency use, Pfizer did not disclose that its trial included only healthy individuals and excluded unhealthy individuals. *See Pfizer and BioNTech Celebrate Historic First Authorization in the U.S. of Vaccine to Prevent COVID-19*, Dec. 11, 2020.[43]

[43] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-celebrate-historic-first-authorization.

111. In its press release announcing emergency use authorization of its COVID-19 vaccine, Pfizer claimed that a "primary endpoint" of the trial of its COVID-19 vaccine was "prevention of COVID-19 regardless of whether participants have previously been infected by SARS-CoV-2." *Id.*

112. Pfizer's statement was misleading since it had excluded any individual who had been diagnosed with COVID-19 from its vaccine trial.

113. In its press release announcing emergency use authorization of its COVID-19 vaccine, Pfizer did not disclose that it had excluded immunocompromised individuals from its COVID-19 vaccine trials. *See id.*

114. Instead, in "Important Safety Information" in its press release, Pfizer noted that "[i]mmunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer BioNTech COVID-19 Vaccine." *Id.*

115. Because it excluded immunocompromised individuals from its COVID-19 vaccine trials, Pfizer did not have a reasonable basis to make representations about the possible effect its COVID-19 vaccine would have on immunocompromised individuals.

116. In its press release announcing emergency use authorization of its COVID-19 vaccine, Pfizer did not disclose that it had excluded pregnant or breastfeeding women from its COVID-19 vaccine trials. *See id.*

117. Instead, Pfizer reported that it planned additional studies to evaluate its COVID-19 vaccine in pregnant women. *Id.*

118. In addition, in "Important Safety Information" in its press release, Pfizer reported, "[a]vailable data on Pfizer BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy." *Id.*

119. Pfizer also reported, "[d]ata are not available to assess the effects of Pfizer BioNTech COVID-19 Vaccine on the breastfed infant or on milk production/excretion." *Id.*

120. Pfizer did not disclose that data was insufficient and unavailable to assess the effects of Pfizer's COVID-19 vaccine on pregnant and breastfeeding women because Pfizer excluded all pregnant and breastfeeding women from its COVID-19 vaccine trials.

121. Six months after vaccinating individuals in its COVID-19 vaccine trial, Pfizer issued another press release that again failed to disclose that Pfizer excluded all unhealthy individuals, immunocompromised individuals, and women who are pregnant or breastfeeding from its COVID-19 vaccine trial. *Pfizer and BioNTech Confirm High Efficacy and No Serious Safety Concerns Through Up to Six Months Following Second Dose in Updated Topline Analysis of Landmark COVID-19 Vaccine Study*, Apr. 1, 2021.[44]

122. Pfizer's April 1, 2021 press release contains the same statements about immunocompromised individuals and women who are pregnant or breastfeeding as its December 11, 2020 press release.

123. Pfizer made representations about its COVID-19 vaccine's safety knowingly or with reason to know that it did not possess a reasonable basis to represent that it was safe for individuals who had been diagnosed with COVID-19, who were immunocompromised, or who were pregnant or breastfeeding.

124. Pfizer made representations knowingly or with reason to know that the safety of its COVID-19 vaccine had not been proven or otherwise substantiated in individuals who had been diagnosed with COVID-19, who were immunocompromised, or who were pregnant or

[44] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious.

breastfeeding. Pfizer did not rely upon or possess the type and amount of proof or substantiation it represented to exist.

125. Pfizer's decision to exclude individuals who had been diagnosed with COVID-19, who were immunocompromised, or who were pregnant or breastfeeding from its vaccine trials were material facts to Kansans making decisions about COVID-19 vaccination.

126. On multiple occasions, Pfizer willfully concealed, suppressed, or omitted material facts about who it had excluded from its COVID-19 vaccine trials, and how those exclusions might affect Pfizer's safety representations.

C. Pfizer's knowledge of COVID-19 vaccine safety issues

127. Pfizer possessed data presenting significant safety concerns associated with its COVID-19 vaccine when Pfizer made public statements in 2021 that its COVID-19 vaccine was safe. *See* Worldwide Safety and Pfizer, *5.3.6 Cumulative Analysis of Post-Authorization Adverse Event Reports of PF-07302048 (BNT162B2) Received Through 28-Feb-2021*, approved Apr. 30, 2021 ("Pfizer Feb. 28, 2021 Adverse Event Data").[45]

128. The FDA defines an adverse event as "any undesirable experience associated with the use of a medical product in a patient." FDA, *What is a Serious Adverse Event?*, content current as of May 18, 2023.[46]

129. The FDA and CDC co-manage the Vaccine Adverse Event Reporting System (VAERS), "a national early warning system to detect possible safety problems in U.S.-licensed vaccines." U.S. Dept. of Health & Human Servs., *About VAERS*.[47]

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[45] *Available at* https://phmpt.org/wp-content/uploads/2022/04/reissue_5.3.6-postmarketing-experience.pdf.
[46] *Available at* https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event.
[47] *Available at* https://vaers.hhs.gov/about.html.

130. VAERS is a passive reporting system that relies on reports submitted by patients and health care providers, "a system that is believed to miss many potential side effects." JoNel Aleccia, *COVID vaccine safety system has gaps that may miss unexpected side effects, experts say*, NBC NEWS (May 2, 2021).[48]

131. Separate from VAERS, Pfizer maintained its own adverse events database that "contain[ed] cases of [adverse events (AEs)] reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious AEs reported from clinical studies regardless of causality assessment." Pfizer Feb. 28, 2021 Adverse Event Data, at 5.

132. Upon information and belief, Pfizer's adverse events database contained more adverse event data than VAERS because it included both information in VAERS and information not in VAERS.

133. Pfizer did not publicly release adverse events data from its database.

134. The Pfizer Feb. 28, 2021 Adverse Event Data document was only obtained through the Public Health and Medical Professionals for Transparency in America FOIA litigation.

135. As of February 28, 2021, Pfizer's adverse events database contained 158,893 adverse events (from 42,086 case reports) from its COVID-19 vaccine. *Id.* at 6.

136. As of February 28, 2021, Pfizer's database contained 1,223 fatalities after taking Pfizer's COVID-19 vaccine, although Pfizer did not make causality findings. *Id.* at 7.

137. Pfizer was receiving so many adverse event reports that it had to hire 600 additional full-time staff and expected to hire more than 1,800 additional resources by June 2021. *Id.* at 6.

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[48] Available at https://www.nbcnews.com/health/health-news/covid-vaccine-safety-system-has-gaps-may-miss-unexpected-side-n1265986.

138. Pfizer had such a backlog of adverse events that it might take 90 days to code "non-serious cases." *Id.*

139. Pfizer did not know "the magnitude of underreporting" *id.* at 5, but significant underreporting was likely. *See* Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29(5):385-96. doi: 10.2165/00002018-200629050-00003. PMID: 16689555 (systematic review of 37 studies concluding that the median under-reporting of adverse drug reactions to spontaneous reporting systems was 94%).

140. Pfizer's representations that its COVID-19 vaccine did not have any safety concerns was inconsistent with the adverse events data it possessed.

141. Pfizer concealed, suppressed, or omitted material facts it possessed showing significant safety concerns associated with Pfizer's COVID-19 vaccine.

D. Pfizer's knowledge of the safety of its COVID-19 vaccine on pregnant women

1. The concerning findings in Pfizer's secret animal study.

142. While Pfizer tested its COVID-19 vaccine on healthy individuals in 2020, Pfizer and its partner BioNTech also quietly tested its COVID-19 vaccine on pregnant rats from June 29, 2020 to October 12, 2020. Charles River, "A Combined Fertility and Development Study (Including Teratogenicity and Postnatal Investigations) of BNT162b1, BNT162b2 and BNT162b3 by Intramuscular Administration in the Wistar Rat," approved Dec. 22, 2020 ("Pfizer Rat Fertility Study"), at 13.[49]

[49] *Available at* https://pdata0916.s3.us-east-2.amazonaws.com/pdocs/110122/125742_S1_M4_20256434.pdf.

143. According to the lab that performed the research, "[t]he rat genome is comparable to the human genome, which makes rats desirable models for the study of diseases that affect humans." Charles River, *Laboratory Rats*.[50]

144. The rat fertility study contained a positive conclusion: "Intramuscular administration of BNT162b1, BNT162b2 and BNT162b3 before and during gestation to female Wistar (CRL:WI[Han]) rats was associated with non-adverse effects (body weight, food consumption and effects localized to the injection site) after each dose administration. There were no effects of any of the 3 vaccine candidates on mating performance or fertility in F0 female rats or on embryo-fetal or postnatal survival, growth, or development of the F1 offspring." Pfizer Rat Fertility Study, at 38.

145. The rat fertility study's details tell a much more concerning story.

146. Rats that received BNT162b2, Pfizer's COVID-19 vaccine:

a. Had multiple fetuses with severe soft tissue and skeletal malformations, *id.* at 34;

b. Did not become pregnant, *id.* at 22 Text Table 5, n. b;

c. Failed to implant embryos at more than double (9.77%) the rate of the control group (4.09%), *id.* at 33;

d. Lost body weight, *id.* at 31; and

e. Consumed less food, *id*.

147. Rats that received other variations of Pfizer's COVID-19 vaccine experienced these issues and others, such as losing their entire litters and delivering stillborn offspring. *Id.* at 30.

148. Pfizer did not issue a press release announcing the rat fertility study's findings.

[50] *Available at* https://www.criver.com/products-services/research-models-services/animal-models/rats?region=3616.

149. Pfizer did not publish a study relating to the rat fertility study's findings.

150. Pfizer issued press releases and published studies for other animal study findings relating to its COVID-19 vaccine. *See, e.g.*, *Pfizer and BioNTech Public Preclinical Data from Investigational COVID-19 Vaccine Program in Nature*, Feb. 1, 2021.[51]

151. Pfizer's rat study was not publicly released until November 2022 in the Public Health and Medical Professionals for Transparency in America FOIA lawsuit.

2. Pfizer announces study on pregnant women but omits material facts already in its possession.

152. On February 18, 2021, Pfizer announced "that the first participants have been dosed in a global Phase 2/3 study to further evaluate the safety, tolerability, and immunogenicity of the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) in preventing COVID-19 in healthy pregnant women 18 years of age and older." *Pfizer and BioNTech Commence Global Clinical Trial to Evaluate COVID-19 Vaccine in Pregnant Women*, Feb. 18, 2021.[52]

153. In its February 18, 2021 press release, Pfizer did not disclose material facts relating to pregnancy in its possession. *See* Pfizer, *Pregnancy and Lactation Cumulative Review*, approved Apr. 20, 2021 ("Pfizer Feb. 28, 2021 Pregnancy Data");[53] *see also* Pfizer Feb. 28, 2021 Adverse Event Data, *supra*, at 12; Pfizer Rat Fertility Study; *supra*.

154. As of February 28, 2021, Pfizer possessed reports for 458 pregnant women exposed to its COVID-19 vaccine during pregnancy. Pfizer Feb. 28, 2021 Pregnancy Data, at 2.

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[51] *Available at* https://cdn.pfizer.com/pfizercom/2021-02/BNT162_Nature_Preclinical_Data_Publication_Statement_to_Upload_VF.pdf.
[52] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-commence-global-clinical-trial-evaluate.
[53] *Available at* https://www.phmpt.org/wp-content/uploads/2023/04/125742_S2_M1_pllr-cumulative-review.pdf.

155. More than half of the pregnant women (248 cases, or 54%) reported an adverse event from Pfizer's COVID-19 vaccine, while fewer than half (210 cases, or 46%) did not report an adverse event. *Id.* at 2-3.

156. More than 1-in-10 women (52) who received Pfizer's COVID-19 vaccine during their pregnancy reported a miscarriage, many within days of vaccination. *Id.* at 3-4.

157. Six women who received Pfizer's COVID-19 vaccine during their pregnancy reported premature deliveries; several babies died. *Id.* at 3.

158. Pfizer's February 18, 2021 press release also did not disclose other adverse effects on the reproductive systems of women who received Pfizer's COVID-19 vaccine.

159. For example, by April 2022, Pfizer knew of tens of thousands of adverse events connected to its COVID-19 vaccine including heavy menstrual bleeding (27,685); menstrual disorders (22,145); irregular periods (15,083); delayed periods (13,989); absence of periods (11,363); and other reproductive system effects. Pfizer, *Appendix 2.1 Cumulative Number of Case Reports (Serious and Non-Serious, Medically Confirmed and Non Medically-Confirmed) from Post-Marketing Data Sources, Overall, by Sex, Country, Age Groups and in Special Populations and Summary Tabulation by Preferred Term and MedDRA System Organ Class*, approved May 6, 2022, at 333-340 (PDF pp. 6-13).[54]

160. Upon information and belief, Pfizer possessed many reports on these adverse events relating to women's reproductive systems at the time of its February 18, 2021 press release.

3. Pfizer's study on pregnant women failed and the results are secret.

[54] *Available at* https://www.tga.gov.au/sites/default/files/2022-08/foi-3727-01.pdf.

161. According to Pfizer's February 18, 2021 press release, Pfizer sought to study approximately 4,000 healthy pregnant women. *Pfizer and BioNTech Commence Global Clinical Trial to Evaluate COVID-19 Vaccine in Pregnant Women*, Feb. 18, 2021.[55]

162. However, Pfizer only enrolled a fraction of this amount (683) in its study. National Library of Medicine, *To Evaluate the Safety, Tolerability, and Immunogenicity of BNT162b2 Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older*, ID NCT04754594, last update posted July 13, 2023.[56]

163. Upon information and belief, Pfizer destroyed the placebo control group during the study, preventing Pfizer from evaluating differences in safety and efficacy between vaccinated pregnant women and unvaccinated pregnant women.

164. Although Pfizer completed its study of its COVID-19 vaccine on pregnant women on July 15, 2022, it still has not completed the quality control review process for the study. *Id.* at Results Submitted.[57]

E. Pfizer's misrepresentations about its COVID-19 vaccine and safety signals

165. On January 18, 2023, when asked whether the Pfizer COVID-19 vaccine caused strokes or myocarditis, Pfizer Chairman and CEO Dr. Bourla said, "We constantly review and analyze the data. We've seen not a single [safety] signal although we have distributed billions of doses." *Pfizer CEO Albert Bourla discusses new vaccines in the pipeline*, CNBC, Jan. 18, 2023, 3:18.[58]

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[55] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-commence-global-clinical-trial-evaluate.
[56] *Available at* https://clinicaltrials.gov/study/NCT04754594.
[57] *Available at* https://clinicaltrials.gov/study/NCT04754594?tab=results.
[58] *Available at* https://www.cnbc.com/video/2023/01/18/pfizer-ceo-albert-bourla-discusses-new-vaccines-to-be-released.html.

166. The FDA has defined "safety signal" as "a concern about an excess of adverse events compared to what would be expected to be associated with a product's use." A "single well-documented case report can be viewed as a signal, …" U.S. Department of Health and Human Services et al., *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, Mar. 2005, at 4 (PDF p. 7).[59]

167. Upon information and belief, contrary to Pfizer Chairman and CEO Dr. Bourla's representations, Pfizer has been aware of numerous safety signals relating to its COVID-19 vaccine.

1. Pfizer's knowledge of a safety signal for myocarditis and pericarditis

168. Upon information and belief, at the time Pfizer Chairman and CEO Dr. Bourla represented that Pfizer had not seen a single safety signal, Pfizer was aware of a safety signal for myocarditis and pericarditis caused by its COVID-19 vaccine.

169. "Myocarditis is inflammation of the heart muscle, and pericarditis is inflammation of the outer lining of the heart." CDC, *Myocarditis and Pericarditis After mRNA COVID-19 Vaccination*, Nov. 3, 2023.[60]

170. From the start, a clear connection existed between Pfizer's COVID-19 vaccine and cases of myocarditis and pericarditis.

i. The United States military detected a safety signal for myocarditis.

171. In early 2021, the U.S. military noticed cases of myocarditis in male military members occurring within four days of administration of Pfizer's COVID-19 vaccine. Report to the Committee on Armed Services of the House of Representatives, *Department of Defense Report*

[59] *Available at* https://www.fda.gov/media/71546/download.
[60] *Available at* https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html.

on Cardiac and Kidney Issues in Service Members Prior to and Following the COVID Vaccine Requirement, Sept. 2023 ("DOD COVID Vaccine Report"), 3;[61] Patricia Kime, *Pentagon Tracking 14 Cases of Heart Inflammation in Troops After COVID-19 Shots*, MILITARY.COM (Apr. 26, 2021).[62]

172. By June 2021, military doctors found an association between the COVID-19 vaccine and myocarditis in at least 23 military patients who had no known cardiac issues until 12 to 96 hours following a mRNA COVID-19 vaccination, after which they developed myocarditis. Jay Montgomery *et al.*, *Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military*, JAMA Cardiol. 2021;6(10):1202-1206. doi:10.1001/jamacardio.2021.2833.[63]

173. When the Department of Defense reviewed its health system data for 2021, it found that "[t]hose who were recently vaccinated had a rate ratio that showed their incidences of myocarditis and pericarditis were 2.6 and 2.0 times higher compared to those who were never vaccinated." DOD COVID Vaccine Report, *supra*, 10.

ii. The United States government detected a safety signal for myocarditis.

174. On March 3, 2021, Israel's Ministry of Health contacted the CDC about myocarditis and pericarditis connected to Pfizer's COVID-19 vaccine: "We are seeing a large number of myocarditis and pericarditis cases in young individuals soon after Pfizer COVID-19 vaccine. We would like to discuss the issue with a relevant expert at CDC."

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[61] *Available at* https://www.health.mil/Reference-Center/Reports/2023/09/29/DOD-Report-on-Cardiac-and-Kidney-Issues-in-Service-Members-Prior-to-and-Following-the-COVID-Vaccine-Requirement.
[62] *Available at* https://www.military.com/daily-news/2021/04/26/pentagon-tracking-14-cases-of-heart-inflammation-troops-after-covid-19-shots.html.
[63] *Available at* https://jamanetwork.com/journals/jamacardiology/fullarticle/2781601.

175. Israel had been tracking myocarditis cases arising shortly after receipt of Pfizer's COVID-19 vaccine. Maayan Jaffe-Hoffman, *19-year-old hospitalized in ICU days after receiving second Pfizer vaccine*, THE JERUSALEM POST (Feb. 1, 2021).[64]

176. Upon information and belief, Pfizer had knowledge of the medical reports in Israel related to its vaccine and myocarditis and pericarditis because Israel agreed to share medical data with Pfizer. Daniel Estrin, *Vaccines for Data: Israel's Pfizer Deal Drives Quick Rollout – And Privacy Worries*, NPR (Jan. 31, 2021);[65] Real-World Epidemiological Evidence Collaboration Agreement, Jan. 6, 2021, §§ 1.8, 2.3, 3, Ex. A.[66]

177. On June 1, 2021, a CDC Advisory Committee on Immunization Practices work group issued a notice stating "that within 30 days of receiving the second dose of either Pfizer or Moderna vaccines, 'there was a higher number of observed than expected myocarditis/pericarditis cases in 16-24-year-olds.'" Elizabeth Cohen, *A link between COVID-19 vaccination and a cardiac illness may be getting closer*, CNN (June 10, 2021).[67]

178. A Pfizer spokesperson provided a statement that said "the company is aware of the myocarditis reports, and that 'a causal link to the vaccine has not been established.'" *Id.*

179. Also on June 1, 2021, Israel's Ministry of Health reported that "it had found the small number of heart inflammation cases observed mainly in young men who received Pfizer's

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[64] *Available at* https://www.jpost.com/health-science/19-year-old-hospitalized-with-heart-inflammation-after-pfizer-vaccination-657428.
[65] *Available at* https://www.npr.org/2021/01/31/960819083/vaccines-for-data-israels-pfizer-deal-drives-quick-rollout-and-privacy-worries.
[66] *Available at* https://www.gov.il/BlobFolder/news/17012021-02/he/files_publications_corona_pfizer_agreement.pdf.
[67] *Available at* https://www.cnn.com/2021/06/09/health/myocarditis-covid-vaccination-link-clearer/index.html.

COVID-19 vaccine in Israel were likely linked to their vaccination." Jeffrey Heller, *Israel sees probable link between Pfizer vaccine and myocarditis cases*, Reuters (June 2, 2021).[68]

180. After the CDC had received 1,200 reports of heart inflammation relating to the COVID-19 vaccine, in late June 2021, the FDA added a warning about the risk of myocarditis and pericarditis to the Pfizer (and Moderna) COVID-19 vaccine fact sheet. Lauren Mascarenhas, *FDA adds a warning to COVID-19 vaccines about risk of heart inflammation*, CNN, June 26, 2021.[69]

181. According to a September 2021 FDA briefing document, "[p]ost-EUA safety surveillance reports received by FDA and CDC identified serious risks for myocarditis and pericarditis following administration of the primary series (Dose 1 and Dose 2)" of Pfizer's COVID-19 vaccine. *Vaccines and Related Biological Products Advisory Committee Meeting, Sept. 17, 2021, FDA Briefing Document, Application for licensure of a booster dose for COMIRNATY (COVID-19 Vaccine, mRNA)*, 7.[70]

182. According to a presentation to the CDC's Advisory Committee in Immunization Practices, analysis through May 2022 found a safety signal for myocarditis and pericarditis (as well as acute myocardial infarction and venous thromboembolism). Nicola Klein, *COVID-19 Vaccine Safety Surveillance: Summary from VSD RCA*, CDC Advisory Committee in Immunization Practices (Sept. 12, 2023), at 42.[71]

183. At the time of Pfizer Chairman and CEO Dr. Bourla's January 18, 2023 denial of any safety signals, the CDC's website reported that "[d]ata from multiple studies show a rare risk for myocarditis and/or pericarditis following receipt of mRNA COVID-19 vaccines. These rare

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[68] *Available at* https://www.reuters.com/world/middle-east/israel-sees-probable-link-between-pfizer-vaccine-small-number-myocarditis-cases-2021-06-01/.
[69] *Available at* https://www.cnn.com/2021/06/25/health/fda-covid-vaccine-heart-warning/index.html.
[70] *Available at* https://www.fda.gov/media/152176/download.
[71] *Available at* https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-09-12/07-covid-klein-508.pdf.

cases of myocarditis or pericarditis have occurred most frequently in adolescent and young adult males, ages 16 years and older, within 7 days after receiving the second dose of an mRNA COVID-19 vaccine (Pfizer-BioNTech and Moderna)." CDC, *Clinical Considerations: Myocarditis and Pericarditis after Receipt of mRNA COVID-19 Vaccines Among Adolescents and Young Adults* (captured Jan. 17, 2023).[72]

184. The CDC currently reports "a causal association between mRNA COVID-19 vaccines (i.e., Moderna or Pfizer-BioNTech) and myocarditis and pericarditis." CDC, *Clinical Considerations: Myocarditis and Pericarditis after Receipt of COVID-19 Vaccines Among Adolescents and Young Adults* (last reviewed Oct. 10, 2023).[73]

iii. Pfizer detected a safety signal for myocarditis.

185. According to a leaked confidential February 2022 Pfizer document, "[s]ince April 2021, increased cases of myocarditis and pericarditis have been reported in the United States after mRNA COVID-19 vaccination (Pfizer-BioNTech and Moderna), particularly in adolescents and young adults (CDC 2021)." Pfizer, *Myocarditis/Pericarditis After mRNA COVID-19 Vaccine Administration: Potential Mechanisms and Recommended Future Actions*, Feb. 11, 2022, at 18.[74]

186. After Pfizer obtained FDA approval through emergency use authorization to provide its COVID-19 vaccine to 12-15-year-olds in August 2021, Pfizer decided to study "how often" its vaccine may cause myocarditis or pericarditis in children by testing 5-16-year-olds for troponin I. *CT05-GSOP-RF05 7.0 Phase 1/2/3/4 Informed Consent Pediatric Study Template,*

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[72] *Available at* https://web.archive.org/web/20230117155359/https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html.
[73] *Available at* https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html.
[74] *Available at* https://downloads.ctfassets.net/syq3snmxclc9/7AqXvmHTBMFOxeGxwMBxxS/7d21477d2697da8adf980ccce52b983f/3-16-23_-_Pfizer_Docs_Watermarked.pdf.

Phase 2/3 Obtaining Serum Samples for Potential Troponin I Testing (all age groups, Pfizer (Sept. 13, 2021), 2.[75]

187. Troponin I, an enzyme in the heart muscle, "could be an early sign of two conditions that affect the heart called myocarditis or pericarditis." *Id.*

188. Pfizer warned children participants that after receiving Pfizer's COVID-19 vaccine, "[y]ou might get chest pain, shortness of breath, or feelings of having a fast-beating, fluttering or pounding heart. You may need to come in to see the study doctor for further assessments if you have these symptoms." *Id.* at 8.

189. Pfizer press releases did not disclose an increased risk of myocarditis from Pfizer's COVID-19 vaccine until November 2021. *Posts falsely claim Pfizer 'officially admits' heart inflammation is COVID jab side effect in 2023*, AFP FRANCE (Dec. 11, 2023).[76]

190. Upon information and belief, at the time of Pfizer Chairman and CEO Dr. Bourla's January 2023 representation that Pfizer had not observed a single safety signal related to Pfizer's COVID-19 vaccine, Pfizer was aware of a safety signal relating to myocarditis and pericarditis.

2. Pfizer's knowledge of a safety signal for strokes

191. Upon information and belief, Pfizer also detected a safety signal relating to strokes.

192. Days before Pfizer Chairman and CEO Dr. Bourla denied any safety signal, the CDC's and FDA's "surveillance system flagged a possible link between the new Pfizer-BioNTech bivalent COVID-19 vaccine and strokes in people aged 65 and over, . . ." Ben Leonard and Lauren

[75] *Available at* https://www.phmpt.org/wp-content/uploads/2023/10/019736_S488_M5_c4591007-p2-3-older-children-assent-troponin-icd.pdf.
[76] *Available at* https://factcheck.afp.com/doc.afp.com.346Z3GD.

Gardner, *CDC, FDA see possible link between Pfizer's bivalent shot and strokes*, POLITICO, Jan. 13, 2023.[77]

193. Although CDC later suggested a link was "very unlikely," a FDA study found that individuals 85 years or older who received both a flu vaccine and Pfizer's COVID-19 vaccine "saw a 20 percent increase in the risk of ischemic stroke." Apoorva Mandavilli, *COVID Shots May Slightly Raise Stroke Risk in the Oldest Recipients*, THE NEW YORK TIMES (Oct. 24, 2023).[78]

194. Pfizer inadequately studied its vaccine's effects on the elderly.

195. When Pfizer sought approval for a third shot—a "booster"—for its COVID-19 vaccine, it requested approval to vaccinate individuals 16 years of age and older, including the elderly. However, Pfizer only tested the booster shot on 12 trial participants who were in the 65- to 85-year-old age range. Vaccines and Related Biological Products Advisory Committee Meeting, Sept. 17, 2021, FDA Briefing Document, Application for licensure of a booster dose for COMIRNATY (COVID-19 Vaccine, mRNA), 22 ("While evaluated in only 12 participants in the age cohort of 65 through 85 years, . . .").[79]

196. Pfizer should not have represented that the booster was "safe" for 65- to 85-year-olds after only testing 12 trial participants in that age range.

197. Pfizer did not test the booster on any participant older than 85 years old. *Id.*

198. Pfizer should not have represented that the booster was "safe" for individuals 85 years old and older when it had not tested any trial participants in that age range.

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[77] *Available at* https://www.politico.com/news/2023/01/13/cdc-fda-pfizer-bivalent-vaccine-possible-strokes-00077933.
[78] *Available at* https://www.nytimes.com/2023/10/24/health/covid-flu-vaccine-stroke.html.
[79] *Available at* https://www.fda.gov/media/152176/download.

199. Upon information and belief, at the time of Pfizer Chairman and CEO Dr. Bourla's representation in January 2023, that Pfizer had not observed a single safety signal related to Pfizer's COVID-19 vaccine, Pfizer was aware of a safety signal relating to strokes.

3. Pfizer's knowledge of a safety signal for increased fatalities

200. Upon information and belief, Pfizer also detected a safety signal relating to deaths.

201. As of February 28, 2021, Pfizer's adverse events database contained 1,223 fatalities after taking Pfizer's COVID-19 vaccine. Pfizer Feb. 28, 2021 Adverse Event Data, *supra*, at 7, table 1.

202. An expert review by the Norwegian Medicines Agency published on May 19, 2021 determined that "[a]mong 100 reported deaths, a causal link to the [Pfizer COVID-19] vaccine was considered probable in 10 cases, possible in 26 and unlikely in 59. Five were unclassifiable." Wyller TB, Kittang BR, Ranhoff AH, Harg P, Myrstad M. Nursing home deaths after COVID-19 vaccination. *Tidsskr Nor Legeforen* 2021;141. doi:10.4045/tidsskr.21.0383.[80]

203. By December 2021, New Zealand's health authorities had linked multiple deaths to Pfizer's COVID-19 vaccine. *New Zealand links 26-year-old man's death to Pfizer COVID-19 vaccine*, REUTERS (Dec. 19, 2021).[81]

204. Upon information and belief, Pfizer was aware of other reports of death related to its COVID-19 vaccine.

205. Upon information and belief, at the time of Pfizer Chairman and CEO Dr. Bourla's representation in January 2023 that Pfizer had not observed a single safety signal related to Pfizer's COVID-19 vaccine, Pfizer was aware of a safety signal relating to deaths.

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[80] *Available at* https://tidsskriftet.no/en/2021/05/originalartikkel/nursing-home-deaths-after-covid-19-vaccination.
[81] *Available at* https://www.reuters.com/world/asia-pacific/new-zealand-links-26-year-old-mans-death-pfizer-covid-19-vaccine-2021-12-20/.

IV. Pfizer Made Unsupported Representations and Concealed Material Facts Relating to Efficacy of its COVID-19 Vaccine.

A. Pfizer misrepresented and concealed material facts relating to the durability of protection provided by its COVID-19 vaccine.

206. In November 2020, Pfizer announced, "[p]rimary efficacy analysis demonstrates BNT162b2 to be 95% effective against COVID-19 beginning 28 days after the first dose." *Pfizer and BioNTech Conclude Phase 3 Study of COVID-19 Vaccine Candidate, Meeting All Primary Efficacy Endpoints*, Pfizer, Nov. 18, 2020.[82]

207. Pfizer did not report the absolute risk reduction of its COVID-19 vaccine, which was just 0.84%. Piero Olliaro *et al.*, *COVID-19 vaccine efficacy and effectiveness—the elephant (not) in the room*, 2 LANCET e279, 279 (July 2021).[83] Absolute risk reduction "measures the precise magnitude and strength of the reduced risk," compared to relative risk reduction that "is a proportion of risk outcomes in separate groups." Brown RB. *Relative risk reduction: Misinformative measure in clinical trials and COVID-19 vaccine efficacy*, at 3. Dialogues Health. 2022 Dec;1:100074. doi: 10.1016/j.dialog.2022.100074. Epub 2022 Nov 10. PMID: 36785641; PMCID: PMC9647013.

208. On February 25, 2021, when asked in an interview how long Pfizer's COVID-19 two-dose vaccine provided protection, Pfizer Chairman and CEO Dr. Bourla stated, "at six months, the protection is robust." *Exclusive interview with Pfizer CEO Albert Bourla*, NBC News (Feb. 25, 2021), at 3:55.[84]

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[82] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine.
[83] *Available at* https://doi.org/10.1016/S2666-5247(21)00069-0.
[84] *Available at* https://www.nbcnews.com/nightly-news/video/exclusive-interview-with-pfizer-ceo-albert-bourla-101605957789.

209. "Robust" is defined as "exhibiting strength" and "capable of performing without failure under a wide range of conditions." Merriam-Webster, *Robust*.[85]

210. Upon information and belief, Pfizer had insufficient data on February 25, 2021 to conclude that protection at six months was robust.

211. On April 1, 2021, Pfizer issued a press release that celebrated "high efficacy" in Pfizer's COVID-19 vaccine through up to six months after the second dose. *Pfizer and BioNTech Confirm High Efficacy and No Serious Safety Concerns Through Up to Six Months Following Second Dose in Updated Topline Analysis of Landmark COVID-19 Vaccine Study*, Pfizer, Apr. 1, 2021.[86]

212. Pfizer represented that "[a]nalysis of 927 confirmed symptomatic cases of COVID-19 demonstrates BNT162b2 is highly effective with 91.3% vaccine efficacy observed against COVID-19, measured seven days through up to six months after the second dose." *Id.*

213. Pfizer cited data in its press release that also appears in a Pfizer efficacy summary document. *2.7.3 Summary of Clinical Efficacy*, approved on Apr. 30, 2021, at 55.[87]

214. Upon information and belief, Pfizer possessed the data contained in the efficacy summary document at the time it published the April 1, 2021 press release.

215. In its efficacy summary document, Pfizer reported an 83.7% efficacy rate four months after the second dose of its COVID-19 vaccine. *Id.* at 68.

216. In its efficacy summary document, Pfizer reported blood sample data showing effectiveness continued to wane at six months. *Id.* at 169, 171.

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[85] *Available at* https://www.merriam-webster.com/dictionary/robust.
[86] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious.
[87] *Available at* https://clinical-information.canada.ca/ci-rc-vu.pdf?file=m2/27-clin-sum/summary-clin-efficacy-covid19-1.pdf&id=252736.

217. Waning effectiveness of Pfizer's COVID-19 vaccine was a material fact for Kansans considering the vaccine.

218. Pfizer did not disclose the material fact of measurable waning effectiveness of its COVID-19 vaccine in its April 1, 2021 press release.

219. Pfizer did not publicly disclose that effectiveness waned to 83.7% until July 28, 2021, in a Pfizer preprint study. Alexa Lardieri, *Pfizer Vaccine Protection Declines After Six Months, Boosters Protect Against Delta Variant*, U.S. News & World Report, July 28, 2021.[88]

220. Pfizer issued a press release on July 28, 2021 that promoted positive results from a booster study, but it did not mention the pre-print study or the waning effectiveness of its COVID-19 vaccine. *Pfizer Reports Second-Quarter 2021 Results*, July 28, 2021, 11.[89]

221. "It's clear from the documents that these analyses were almost four months old by the time they became public," said Peter Doshi, an associate professor at the University of Maryland School of Pharmacy. "It's disappointing that neither Pfizer, nor regulators, disclosed these data until it was too obvious to ignore new outbreaks in Israel and Massachusetts, which made it clear that vaccine performance was not holding up." Maryanne Demasi, *Pfizer Hid Data on Waning Immunity*, Brownstone Institute, Apr. 7, 2023.[90]

222. Pfizer's concealment, suppression, and omission of the waning effectiveness of its COVID-19 vaccine allowed Pfizer to profit from vaccinations of Kansans who may have been deterred from Pfizer's COVID-19 vaccine had they known about its waning effectiveness.

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[88] *Available at* https://www.usnews.com/news/health-news/articles/2021-07-28/pfizer-vaccine-protection-declines-after-six-months-boosters-protect-against-delta-variant.
[89] *Available at* https://s21.q4cdn.com/317678438/files/doc_financials/2021/q2/Q2-2021-PFE-Earnings-Release.pdf.
[90] *Available at* https://brownstone.org/articles/pfizer-hid-data-on-waning-immunity/.

223. Pfizer collected $7.8 billion in direct sales and alliance revenues from its COVID-19 vaccine in the second quarter of 2021, or the time between its April 1, 2021 press release failing to disclose the waning effectiveness of its COVID-19 vaccine and June 30, 2021, more than one month before its belated disclosure on waning effectiveness of its COVID-19 vaccine. *Pfizer Reports Second-Quarter 2021 Results*, July 28, 2021, 5.[91]

B. Pfizer misrepresented and concealed material facts relating to the effectiveness against variants provided by its COVID-19 vaccine.

224. On February 25, 2021, Pfizer Chairman and CEO Dr. Bourla said data suggested that individuals fully vaccinated with Pfizer's COVID-19 vaccine were protected against any variant currently known, including the South African, Brazilian, and UK variants. *Exclusive interview with Pfizer CEO Albert Bourla*, NBC NEWS (Feb. 25, 2021), at 0:15.[92]

225. On June 15, 2021, Pfizer Chairman and CEO Dr. Bourla reiterated his belief that his company's COVID-19 vaccine would protect against variants: "I feel quite comfortable that we cover it. . . . We will not need a special vaccine for it. The current vaccine should cover it." *CEO 'comfortable' Pfizer COVID-19 vaccine protects against more severe Delta variant*, CBS NEWS (June 15, 2021).[93]

226. On June 24, 2021, Pfizer's medical director in Israel reported that Pfizer's COVID-19 vaccine was "very effective, around 90%" against the Delta variant. Maayan Lubell, *Pfizer says COVID vaccine is highly effective against Delta variant*, REUTERS (June 24, 2021).[94]

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[91] *Available at* https://s21.q4cdn.com/317678438/files/doc_financials/2021/q2/Q2-2021-PFE-Earnings-Release.pdf.
[92] *Available at* https://www.nbcnews.com/nightly-news/video/exclusive-interview-with-pfizer-ceo-albert-bourla-101605957789.
[93] *Available at* https://www.cbsnews.com/news/pfizer-vaccine-delta-variant/.
[94] *Available at* https://www.reuters.com/business/healthcare-pharmaceuticals/pfizer-says-covid-vaccine-highly-effective-against-delta-variant-2021-06-24/.

227. But on July 6, 2021, Israel's Health Ministry announced that Pfizer's COVID-19 vaccine effectiveness was just 64%. *Israel sees drop in Pfizer COVID vaccine protection, still strong in severe illness*, REUTERS (July 6, 2021).[95]

228. On July 8, 2021, Pfizer publicly admitted the declining effectiveness of its COVID-19 vaccine after six months post-vaccination and against the Delta variant. *Pfizer and BioNTech Provide Update on Booster Program in Light of the Delta Variant*, Pfizer (July 8, 2021).[96]

229. Pfizer announced it was conducting an "ongoing booster trial of a third dose" of its COVID-19 vaccine and "developing an updated version of the Pfizer-BioNTech COVID-19 vaccine that targets the full spike protein of the Delta variant." *Id.*

230. Upon information and belief, Pfizer already was conducting a booster trial and developing an updated version of its COVID-19 vaccine because, despite its public statements to the contrary, it knew its COVID-19 vaccine was not effective against the Delta variant.

231. Just two weeks later, on July 23, 2021, Israel reported Pfizer's COVID-19 vaccine was only 39% effective. Berkeley Lovelace, *Israel says Pfizer COVID vaccine is just 39% effective as delta spreads, but still prevents severe illness*, CNBC (July 23, 2021).[97]

232. But when contacted for the report about its COVID-19 vaccine's 39% effectiveness, Pfizer continued to misrepresent effectiveness of its COVID-19 vaccine: "In a statement to CNBC, Pfizer said it remains confident its two-dose regimen is protective against the coronavirus and its variants." *Id.*

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[95] *Available at* https://www.reuters.com/world/middle-east/israel-sees-drop-pfizer-vaccine-protection-against-infections-still-strong-2021-07-05/.
[96] *Available at* https://cdn.pfizer.com/pfizercom/2021-07/Delta_Variant_Study_Press_Statement_Final_7.8.21.pdf?IPpR1xZjlwvaUMQ9sRn2FkePcBiRPGqw.
[97] *Available at* https://www.cnbc.com/2021/07/23/delta-variant-pfizer-covid-vaccine-39percent-effective-in-israel-prevents-severe-illness.html.

233. In August 2021, a study "found the Pfizer vaccine was only 42% effective against infection in July, when the Delta variant was dominant." Caitlin Owens, *New data on coronavirus vaccine effectiveness may be 'a wakeup call*,' AXIOS (Aug. 11, 2021).[98]

234. Despite data showing its COVID-19 vaccine was not effective, Pfizer's chief medical officer said in October 2021, "[o]ur variant-specific analysis clearly shows that the BNT162b2 vaccine is effective against all current variants of concern, including delta." Berkeley Lovelace Jr., *Pfizer COVID shot protects people from hospitalization even as effectiveness against infection falls, Lancet study confirms*, CNBC (Oct. 4, 2021).[99]

235. Finally, by December 2021, Pfizer acknowledged potential effectiveness issues with its COVID-19 vaccine and the Omicron variant. "Sera from individuals who received two doses of the current COVID-19 vaccine did exhibit, on average, more than a 25-fold reduction in neutralization titers against the Omicron variant compared to wild-type, indicating that two doses of BNT162b2 may not be sufficient to protect against infection with the Omicron variant." *Pfizer and BioNTech Provide Update on Omicron Variant*, Pfizer (Dec. 8, 2021).[100]

236. Pfizer attempted to soften this news by claiming that two doses still protected against "severe forms of the disease." *Id.*

237. But in January 2022, Pfizer Chairman and CEO Dr. Bourla admitted that the vaccine lost effectiveness at both preventing infections and hospitalizations: "We have seen with a second dose very clearly that the first thing that we lost was the protection against infections. . . . But then two months later, what used to be very strong in hospitalization also went down. And

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[98] *Available at* https://www.axios.com/2021/08/11/coronavirus-vaccines-pfizer-moderna-delta-biden.
[99] *Available at* https://www.cnbc.com/2021/10/04/pfizer-covid-vaccine-protection-against-infection-tumbles-to-47percent-study-confirms.html.
[100] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant.

I think this is what everybody's worried about." Spencer Kimball, *Pfizer CEO says two COVID vaccine doses aren't 'enough for omicron,'* CNBC (Jan. 10, 2022).[101]

238. Pfizer Chairman and CEO Dr. Bourla acknowledged that "two doses, they're not enough for omicron." *Id.*

239. Indeed, United Kingdom data reported that two doses of Pfizer's COVID-19 vaccine "are only about 10% effective at preventing infection from omicron 20 weeks after the second dose." *Id.*

240. Upon information and belief, Pfizer was aware that its COVID-19 vaccine was not effective at preventing infection or hospitalization from variants, such as Delta and Omicron, at the time it was publicly representing the opposite information.

241. The ineffectiveness of Pfizer's COVID-19 vaccine against variants was a material fact.

V. Pfizer Made Unsupported Representations Relating to Transmission of its COVID-19 Vaccine.

A. Pfizer's statements and knowledge about the effect of its COVID-19 vaccine on transmission of COVID-19

242. When the FDA issued the Emergency Use Authorization for Pfizer's COVID-19 vaccine in December 2020, the FDA reported that there was no "evidence that the vaccine prevents transmission of SARS-CoV-2 from person to person." *FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine*, Dec. 11, 2020.[102]

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[101] *Available at* https://www.cnbc.com/2022/01/10/pfizer-ceo-says-two-covid-vaccine-doses-arent-enough-for-omicron.html.

[102] *Available at* https://wayback.archive-it.org/7993/20201217195048/https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19.

243. According to Pfizer's trial protocol, evaluating transmission was not an objective of the trial. Apr. 2020 Protocol, *supra*, 11-12 (PDF pp. 13-14);[103] Sept. 2020 Protocol, *supra*, 10-13 (PDF p. 138-141).[104]

244. Pfizer has publicly confirmed that it did not test its COVID-19 vaccine on stopping transmission. When asked, "Was the Pfizer COVID vaccine tested on stopping the transmission of the virus before it entered the market?" Pfizer's Director of International Developed Markets Janine Small responded, "No." Frank Chung, *Pfizer did not know whether COVID vaccine stopped transmission before rollout, executive admits*, NEWS.COM.AU, Oct. 13, 2022.[105]

245. In November 2020, Pfizer Board Member Dr. Scott Gottlieb reported that more research was needed on transmission after receiving a Pfizer COVID-19 vaccination. "I think initially it's probably going to be given on a general schedule until we learn more about the real-world benefits of the vaccine and how much it cuts down on transmission of the virus. You know, does it just prevent you from getting COVID symptoms or does it actually prevent you from getting the infection and spreading the infection? That's one of the things we're going to need to determine about the vaccine and how long the immunity is." *Full transcript of 'Face the Nation' on November 22, 2020*, CBS NEWS, Nov. 22, 2020.[106]

246. Pfizer Chairman and CEO Dr. Bourla also wanted more transmission research in December 2020. "Even though I've had the protection, am I still able to transmit [COVID-19] to other people?" Bourla told NBC News' Lester Holt. "I think this is something that needs to be examined. We are not certain about that right now with what we know." Joseph Choi, *Pfizer*

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[103] *Available at* https://www.nejm.org/doi/suppl/10.1056/NEJMoa2027906/suppl_file/nejmoa2027906_protocol.pdf.
[104] *Available at* https://www.nejm.org/doi/suppl/10.1056/NEJMoa2027906/suppl_file/nejmoa2027906_protocol.pdf.
[105] *Available at* https://www.news.com.au/technology/science/human-body/pfizer-did-not-know-whether-covid-vaccine-stopped-transmission-before-rollout-executive-admits/news-story/f307f28f794e173ac017a62784fec414.
[106] *Available at* https://www.cbsnews.com/news/full-transcript-of-face-the-nation-on-november-22-2020/.

chairman: We're not sure if someone can transmit virus after vaccination, THE HILL, Dec. 3, 2020.[107]

B. Pfizer's representations that its COVID-19 vaccine would prevent transmission.

247. Despite admissions by Pfizer Chairman and CEO Dr. Bourla and Board Member Dr. Scott Gottlieb that Pfizer did not know if its vaccine prevented transmission, Pfizer Chairman and CEO Dr. Bourla warned Kansans on multiple occasions that not receiving a COVID-19 vaccine would affect the lives of those around them, thus implying that Pfizer's COVID-19 vaccine prevented transmission.

a. December 2020: "I repeat once more, that this choice not to vaccinate will not affect only your health or your life. Unfortunately, it will affect the lives of others and likely the lives of the people you love the most, who are the people that usually you are in contact with." *CNBC Transcript: Pfizer Chairman and CEO Albert Bourla Speaks with CNBC's 'Squawk Box' Today*, CNBC (Dec. 14, 2020).[108]

b. January 2021: "What I would say to people who fear the vaccine is that they need to recognize that the decision to take it or not will not affect only their own lives. It will affect the lives of others. And most likely it will affect the lives of people that they love the most, who are the people that they socialize the most with." John Micklethwait, *Pfizer CEO Says Science Will Prevail with COVID-19 Here to Stay*, BLOOMBERG, Jan. 28, 2021.[109]

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[107] *Available at* https://thehill.com/news-by-subject/healthcare/528619-pfizer-chairman-were-not-sure-if-someone-can-transmit-virus-after/.
[108] *Available at* https://www.cnbc.com/2020/12/14/cnbc-transcript-pfizer-chairman-and-ceo-albert-bourla-speaks-with-cnbcs-squawk-box-today.html.
[109] *Available at* https://www.bloomberg.com/news/features/2021-01-28/covid-is-here-to-stay-pfizer-ceo-albert-bourla.

c. June 2021: "I try to explain to them that the decision to vaccinate or not is not only going to affect only your life. . . . But unfortunately will affect the health of others and likely will affect the health of people you like and you love the most. . . . When you try to explain that their fear could stand in the way of protecting their loved ones, I think this is the argument that mostly works." *CEO 'comfortable' Pfizer COVID-19 vaccine protects against more severe Delta variant*, CBS NEWS (June 15, 2021).[110]

d. November 2021: "The only thing that stands between the new way of life and the current way of life, frankly, is the hesitancy to get vaccinated, the people that are afraid to get the vaccines, and they create issues not only for them. Unfortunately, they are going to affect the lives of others and, frankly, the lives of the people that they love the most because they are putting at risk the people that they hug, they kiss, [and] they socialize with." *Pfizer's Albert Bourla on how the pandemic ends*, ATLANTIC COUNCIL, Nov. 9, 2021.[111]

248. In other words, on multiple occasions, Pfizer Chairman and CEO Dr. Bourla represented to Kansans that Pfizer's COVID-19 vaccine prevented transmission since not getting vaccinated threatened the lives of loved ones with whom a person closely interacted.

249. In December 2021, a Pfizer press release quoted Chairman and CEO Dr. Bourla in a manner that again suggested that Pfizer's COVID-19 vaccine prevented transmission: "Ensuring as many people as possible are fully vaccinated with the first two dose series and a booster remains

[110] *Available at* https://www.cbsnews.com/news/pfizer-vaccine-delta-variant/.
[111] *Available at* https://www.atlanticcouncil.org/blogs/new-atlanticist/pfizers-albert-bourla-on-how-the-pandemic-ends/.

the best course of action **to prevent the spread of COVID-19**." *Pfizer and BioNTech Provide Update on Omicron Variant*, Pfizer (Dec. 8, 2021) (emphasis added).[112]

250. Pfizer Board Member Dr. Scott Gottlieb also represented to Kansans that Pfizer's COVID-19 prevented transmission: "And final point, I mean, some of the optimism is also being driven by growing science, suggesting that these vaccines, all the vaccines not only prevent COVID disease, prevent symptoms, but also prevent transmission. So they could have a dramatic effect on reducing the overall tenor of the epidemic." *Full transcript of 'Face the Nation' on March 7, 2021*, CBS News, Mar. 7, 2021.[113]

251. Pfizer even used comic books to suggest that the vaccine prevented transmission. In 2022, Pfizer partnered with Marvel to produce an "Avengers"-themed comic book that called individuals waiting for a Pfizer COVID-19 vaccine "Everyday Heroes." *See* Avengers: Everyday Heroes, 2022.[114]

252. According to one of the characters in the Pfizer comic book, "it's also important for entire communities to come together and help fight the threat." "And that's exactly what we're doing today!" says another character. As the group heads to the examination room to get their Pfizer COVID-19 vaccinations, the first character announces, "The Avengers are doing their part to help keep us safe. Now it's time for us to do ours." *Id.* at 13.

253. One of the final pages reinforces the need for individuals to get a Pfizer COVID-19 vaccine in order to protect the community. "Everyday heroes don't wear capes! But they do wear a small bandage on their upper arm after they get their latest COVID-19 vaccination—

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[112] *Available at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant.
[113] *Available at* https://www.cbsnews.com/news/full-transcript-of-face-the-nation-on-march-7-2021/.
[114] *Available at* https://www.marvel.com/pfizereverydayheroes#open_text-5/.

because everyday heroes are concerned about their health. **And they're people who choose to unite with their communities and do their part to help protect against COVID-19**." *Id*. at 15 (emphasis added).

254. Pfizer released the "Everyday Heroes" comic book as a digital comic and provided print editions at some offices and retail locations around the country. *Avengers Assemble! Teaming Up with Marvel to Illustrate the Importance of COVID-19 Vaccination*, PFIZER.[115]

255. Pfizer represented that its COVID-19 vaccine could prevent transmission of COVID-19, even though it had no basis for the representation since Pfizer never tested its COVID-19 vaccine to determine whether it could prevent transmission of COVID-19.

256. Pfizer misled Kansans about the effect of the COVID-19 vaccine on transmission of COVID-19.

VI. Pfizer's Efforts to Censor and Suppress Material Facts related to its COVID-19 Vaccines

257. When Pfizer's efforts to hide material facts from public scrutiny failed, Pfizer took action to conceal and suppress material facts related to its COVID-19 vaccines.

A. Pfizer's view that "misinformation spreaders" are "criminals" who have "literally cost millions of lives"

258. A Pfizer website page on "Fighting Misinformation" states: "The spread of rumors and falsehoods can be dangerous. It is a threat to truth that misleads and manipulates people's perceptions. We are dedicated to helping people find accurate, science-based information as they make healthcare decisions that impact their lives." Pfizer, *Fighting Misinformation*.[116]

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[115] *Available at* https://www.pfizer.com/news/articles/avengers_assemble_teaming_up_with_marvel_to_illustrate_the_importance_of_covid_19_vaccination.

[116] *Available at* https://www.pfizer.com/about/responsibility/misinformation.

259. On July 19, 2021, Pfizer Board Member Dr. Scott Gottlieb claimed social media companies had an "obligation" and an "affirmative responsibility" to prevent the spread of COVID-19 vaccine misinformation on their platforms. Pia Singh, *Dr. Scott Gottlieb urges social media platforms to curb COVID vaccine misinformation*, CNBC, July 19, 2021.[117]

260. Pfizer Chairman and CEO Dr. Bourla called people who spread misinformation on COVID-19 vaccines "criminals" who have "literally cost millions of lives." *Pfizer's Albert Bourla on how the pandemic ends*, ATLANTIC COUNCIL, Nov. 9, 2021.[118]

B. Pfizer worked to conceal and suppress material facts.

261. Pfizer worked to conceal and suppress material facts on social media platforms.

262. Pfizer Board Member Dr. Scott Gottlieb pressed Twitter on multiple occasions to censor speech critical of COVID-19 vaccines and the response to the pandemic.

263. On August 24, 2021, Pfizer Board Member Dr. Scott Gottlieb contacted Twitter to complain about a column written by Alex Berenson that criticized Dr. Anthony Fauci. "This is whats [*sic*] promoted on Twitter. This is why Tony needs a security detail," Gottlieb wrote. Charles Creitz, *Alex Berenson says Pfizer-linked former FDA official got him banned from Twitter in 'months-long conspiracy,'* FOX NEWS (Oct. 13, 2022).[119]

264. On August 27, 2021, Pfizer Board Member Dr. Scott Gottlieb had a conference call with Twitter employees to discuss Mr. Berenson. Twitter banned Mr. Berenson the next day.

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[117] *Available at* https://www.cnbc.com/2021/07/19/scott-gottlieb-social-media-must-act-to-curb-covid-vaccine-misinformation.html.
[118] *Available at* https://www.atlanticcouncil.org/blogs/new-atlanticist/pfizers-albert-bourla-on-how-the-pandemic-ends/.
[119] *Available at* https://www.foxnews.com/media/alex-berenson-pfizer-linked-former-fda-official-banned-twitter-months-long-conspiracy.

265. On Friday, August 27, 2021, Dr. Brett P. Giroir, who served as the assistant secretary for health from 2018 to 2021 and approximately one month as the acting FDA Commissioner in late 2019, posted to Twitter that natural immunity was superior to vaccine immunity. Joseph A. Wulfsohn, *Twitter Files: Pfizer board member Dr. Scott Gottlieb flagged tweets questioning COVID vaccine*, FOX NEWS (Jan. 9, 2023).[120]

266. In response, Pfizer Board Member Dr. Scott Gottlieb reached out to Twitter's top lobbyist in Washington, D.C., to complain that the post was "corrosive," "draws a sweeping conclusion," and "will end up going viral and driving news coverage." *Id.*

267. The Twitter lobbyist forwarded Pfizer Board Member Dr. Scott Gottlieb's email to the Twitter "Strategic Response" team, which "later slapped [Girori's tweet] with a 'misleading' label and blocked any ability to like or share the tweet." *Id.*

268. Upon information and belief, Pfizer Board Member Dr. Scott Gottlieb contacted social media platforms to request censorship of other COVID-19-related posts.

269. Upon information and belief, Pfizer coordinated with and through others to conceal and suppress other material facts about its COVID-19 vaccine.

270. On December 11, 2020, the same day that Pfizer's COVID-19 vaccine received emergency use authorization from the FDA, a Zoom calendar appointment entitled "Vaccine Disinformation Response" invited personnel at the Department of Health and Human Services, Pfizer and other pharmaceutical companies, and Stanford University to discuss "a coalition to

[120] *Available at* https://www.foxnews.com/media/twitter-files-pfizer-board-member-dr-scott-gottlieb-flagged-tweets-questioning-covid-vaccine.

respond to COVID-19 vaccine disinformation." Letter from U.S. House Judiciary Chairman Jim Jordan to Pfizer's Dr. Albert Bourla, July 18, 2023, at 1-2.[121]

271. Upon information and belief, at or around this December 11, 2020 meeting, Pfizer, the Department of Health and Human Services, and Stanford University agreed to work together to conceal and suppress material facts about Pfizer's COVID-19 vaccine, including concealing and suppressing posts about the safety and efficacy of Pfizer's COVID-19 vaccine.

272. The CDC is within the Department of Health and Human Services. U.S. Dep't of Health and Human Servs., *HHS Organizational Charts Office of Secretary and Divisions*.[122]

273. In 2021, the CDC actively worked to censor speech critical of COVID-19 vaccines. Robby Soave, *Inside the Facebook Files: Emails Reveal the CDC's Role in Silencing COVID-19 Dissent*, REASON (Jan. 19, 2023).[123]

274. Shortly after the December 11, 2020 meeting, Stanford University co-launched the Virality Project.

275. For at least the next year, Stanford and members of the Virality Project pressured social media companies to conceal and suppress information about Pfizer's COVID-19 vaccine, including information about safety and efficacy. *See general Memes, Magnets, and Microchips: Narrative dynamics around COVID-19 vaccines*, THE VIRALITY PROJECT, Apr. 26, 2022, at 39 (PDF p. 46); 46 (PDF p. 53); 56 (PDF p. 63); 84 (PDF p. 91).[124]

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[121] *Available at* https://judiciary.house.gov/sites/evo-subsites/republicans-judiciary.house.gov/files/evo-media-document/2023-07-18-jdj-to-bourla-pfizer.pdf.
[122] *Available at* https://www.hhs.gov/about/agencies/orgchart/index.html.
[123] *Available at* https://reason.com/2023/01/19/facebook-files-emails-cdc-covid-vaccines-censorship/.
[124] *Available at* https://stacks.stanford.edu/file/druid:mx395xj8490/Virality_project_final_report.pdf.

276. Upon information and belief, the Virality Project flagged supposed "misinformation" to platforms on a massive scale, with a high degree of success in inducing the platforms to censor it.

277. The Virality Project admits that six social-media platforms "engaged with VP tickets," "acknowledge[ed] content flagged for review" by the VP, "and act[ed] on it in accordance with their policies"—in other words, censored it. *Id.* at 18 (PDF p. 25).

278. The Virality Project was not the only organization pressuring social media companies to conceal and suppress speech about Pfizer's COVID-19 vaccine on behalf of Pfizer.

279. The Virality Project partnered with a campaign called "Stronger." Stronger, *About*.[125] Stronger described itself as "a first-of-its-kind national advocacy campaign against misinformation and for vaccines." *National Public Health Campaign Designed to Mobilize Support of Vaccines*, July 15, 2020.[126]

280. Pfizer was a top funder and served as a board member for the group, Biotechnology Innovation Organization, that paid for the Stronger campaign. Lee Fang (@lhfang), Twitter, Jan. 16, 2023 at 11:13 a.m.;[127] Biotechnology Innovation Organization "Helix Sponsor;"[128] John D. Young.[129]

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[125] *Available at* https://stronger.org/about.
[126] *Available at* https://www.prnewswire.com/news-releases/national-public-health-campaign-designed-to-mobilize-support-of-vaccines-301093876.html?tc=eml_cleartime&fbclid=IwAR0y3GEys3DsmxdPz3WDpkvN7iJyA4PsmNh2tWWL7K6d7MdshMSicIvQukc.
[127] *Available at* https://twitter.com/lhfang/status/1615019469516197891.
[128] *Available at* https://www.bio.org/.
[129] *Available at* https://www.novartis.com/about/board-directors/john-d-young

281. According to Stronger, "Our mission is to dispel vaccine misinformation so that more adults get vaccinated, kids receive their routine immunizations, and everybody who can get a COVID-19 vaccine does." Stronger.[130]

282. Stronger "regularly communicated with Twitter on regulating content related to the pandemic. The firm worked closely with the San Francisco social media giant to help develop bots to censor vaccine misinformation and, at times, sent direct requests to Twitter with lists of accounts to censor and verify." Lee Fang, *COVID-19 Drugmakers Pressured Twitter to Censor Activists Pushing for Generic Vaccine*, THE INTERCEPT, Jan. 16, 2023.[131]

283. Upon information and belief, Pfizer worked to conceal and suppress material facts relating to its COVID-19 vaccine.

VII. Pfizer's Record-Breaking COVID-19 Vaccine Profits

284. Pfizer's misrepresentations and suppression, concealment, and omission of material facts paid off handsomely for Pfizer because they allowed Pfizer to acquire and keep market share for its COVID-19 vaccine.

285. In 2020, Pfizer reported more than $9.1 billion in profit. Ryan King, *Pfizer reports nearly $37 billion in COVID-19 vaccine sales in 2021*, WASHINGTON EXAMINER, Feb. 8, 2022.[132]

286. In 2021, Pfizer reported approximately $37 billion in global direct sales and alliance revenue from its COVID-19 vaccine. *Id.*

287. Thanks to Pfizer's COVID-19 vaccine, Pfizer more than doubled its profits from 2020 to 2021, reporting $22 billion in total profits in 2021. *Id.*

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[130] *Available at* https://stronger.org/.
[131] *Available at* https://theintercept.com/2023/01/16/twitter-covid-vaccine-pharma/.
[132] *Available at* https://www.washingtonexaminer.com/policy/healthcare/pfizer-reports-nearly-37-billion-in-covid-19-vaccine-sales-in-2021.

288. In 2022, Pfizer reported approximately $38 billion in global direct sales and alliance revenue from its COVID-19 vaccine. Spencer Kimball, *The COVID pandemic drives Pfizer's 2022 revenue to a record $100 billion*, CNBC, Jan. 31, 2023.[133]

289. Overall, Pfizer reported a record $100 billion in revenue in 2022. *Id.* Pfizer's COVID-19 vaccine made up approximately 40% of Pfizer's total revenue.

290. Pfizer made record-breaking profits because it misrepresented, suppressed, concealed, and omitted material facts relating to its COVID-19 vaccine.

291. Pfizer's profit would have been lower if Pfizer had not misrepresented, suppressed, concealed, and omitted material facts relating to its COVID-19 vaccine.

VIII. Pfizer's Violation of Past Consent Judgments with the State of Kansas

292. Pfizer entered consent judgments with the State of Kansas to resolve consumer protection claims that govern Pfizer's future conduct, including relating to its COVID-19 vaccine.

A. The 2008 Consent Judgment

293. In 2008, Pfizer paid $60 million to resolve claims by a group of states, including Kansas, relating to Pfizer's promotional and marketing practices regarding the prescription drugs Celebrex® and Bextra®. Final Consent Judgment, *State of Kansas, ex rel. Steve Six v. Pfizer Inc.*, No. 08CV1576 (Oct. 23, 2008), attached as Exhibit A.

294. According to the 2008 Consent Judgment, "Pfizer shall not make any written or oral claim that is false, misleading or deceptive regarding any FDA-approved Pfizer Product." *Id.* at ¶ 4.

[133] *Available at* https://www.cnbc.com/2023/01/31/the-covid-pandemic-drives-pfizers-2022-revenue-to-a-record-100-billion.html.

295. The 2008 Consent Judgment defined "Product" to mean "any prescription drug or biological product manufactured, distributed, sold, marketed or promoted in the United States in any way." *Id.* at § 2, ¶ 5(l).

296. While the 2008 Consent Judgment does not define "biological product," the FDA defines "biological product" to include vaccines. FDA, *What Are "Biologics" Questions and Answers*, content current as of Feb. 6, 2018;[134] *see also* 42 U.S.C. § 262.

297. Under the 2008 Consent Judgment, Pfizer's COVID-19 vaccine is a biological product manufactured, distributed, sold, marketed or promoted in the United States in any way.

298. Pfizer received FDA approval for its COVID-19 vaccine, including but not limited to through an emergency use authorization on December 11, 2020 for individuals 16 years old and older; through an amended emergency use authorization on May 10, 2021 for children 12 years old to 15 years old; through full approval on August 23, 2021 for individuals 16 years old and older; through emergency use authorization on October 29, 2021 for children five years old to 11 years old; through emergency use authorization on June 17, 2022 for children 6 months through four years; and through full approval on July 8, 2022 for children 12 through 15 years of age.

299. The 2008 Consent Judgment also governs communications about clinical studies of Pfizer's COVID-19 vaccine.

300. According to the 2008 Consent Judgment:

> When presenting information in detailing pieces, brochures, booklets, mailing pieces, published journals, magazines, other periodicals and newspapers, and broadcast through media such as radio, television, the Internet, and telephone communications systems, about a Clinical Study that relates to an FDA-approved Pfizer Product, Pfizer shall: (a) accurately reflect the methodology

[134] *Available at* https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers.

> used to conduct the Clinical Study; (b) not present favorable information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions; and (c) not use statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluation.

Id. at ¶ 10; *see also* ¶ 12.

301. Similarly, according to the next paragraph in the 2008 Consent Judgment:

> When presenting information in detailing pieces, brochures, booklets, mailing pieces, published journals, magazines, other periodicals and newspapers, and broadcast through media such as radio, television, the Internet, and telephone communications systems, about a Clinical Study or analysis of Clinical Studies as evidence of an FDA-approved Pfizer Product's safety, Pfizer shall not: (a) present information from a study in a way that implies that the study represents larger or more general experience with the drug than it actually does; or (b) use statistics on numbers of patients, or counts of favorable results or side effects derived from pooling data from various insignificant or dissimilar studies in a way that suggests either that such statistics are valid if they are not or that they are derived from large or significant studies supporting favorable conclusions when such is not the case.

Id. at ¶ 11.

302. As set forth in the 2008 Consent Judgment, *id.* at ¶ 35, the Kansas Attorney General provided Pfizer notice of his reasonable belief that Pfizer has engaged in practices that violate the 2008 Consent Judgment. Letter from Kansas Attorney General's Office to Pfizer Inc., Apr. 22, 2024, attached as Exhibit B.

303. In response to the notice from Plaintiff Kansas Attorney General, Pfizer did not address all of the issues identified by Plaintiff, did not respond to evidence cited by Plaintiff, and did not produce documents requested by Plaintiff. Letter from Pfizer's Counsel to Kansas Attorney General's Office, May 22, 2024, attached as Exhibit C.

304. The 2008 Consent Judgment empowers the Kansas Attorney General to assert any claim that Pfizer has violated this Judgment in a separate civil action and to enforce compliance with the Consent Judgment and to seek any other relief afforded by law, pursuant to K.S.A. 50-636(b). Ex. A, at ¶ 36.

B. The 2012 Consent Judgment

305. In 2012, Pfizer paid $42.9 million to resolve claims by a group of states, including Kansas, relating to Pfizer's promotional and marketing practices regarding the prescription drugs Zyvox® and Lyrica®. Final Consent Judgment, *State of Kansas, ex rel. Derek Schmidt v. Pfizer Inc.*, No. 12CV1339 (Dec. 13, 2012), attached as Exhibit D.

306. According to the 2012 Consent Judgment, "Pfizer shall not make, or cause to be made, any written or oral claim that is false, misleading, or deceptive regarding any FDA-approved Pfizer Product, . . ." *Id.* at ¶ 3.1.

307. The 2012 Consent Judgment defined "Pfizer Product" to mean "any FDA-approved prescription drug or biological product manufactured, distributed, sold, marketed or Promoted by Pfizer in the United States." *Id.* at ¶ 2.18.

308. While the 2012 Consent Judgment does not define "biological product," the FDA defines "biological product" to include vaccines. FDA, *What Are "Biologics" Questions and Answers*, content current as of Feb. 6, 2018;[135] *see also* 42 U.S.C. § 262.

309. Under the 2012 Consent Judgment, Pfizer's COVID-19 vaccine is a biological product manufactured, distributed, sold, marketed or Promoted in the United States.

[135] *Available at* https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers.

310. Pfizer's COVID-19 vaccine received FDA approval beginning on December 11, 2020.

311. As set forth in the 2012 Consent Judgment, *id.* at ¶ 6.1, the Kansas Attorney General provided Pfizer notice of his reasonable belief that Pfizer has engaged in practices that violate the 2012 Consent Judgment. *See* Ex. B.

312. In response to the notice from Plaintiff Kansas Attorney General, Pfizer did not address all of the issues identified by Plaintiff, did not respond to evidence cited by Plaintiff, and did not produce documents requested by Plaintiff. *See* Ex. C.

313. The 2012 Consent Judgment empowers the Kansas Attorney General to assert any claim that Pfizer has violated this Judgment in a separate civil action and to enforce compliance with the Consent Judgment and to seek any other relief afforded by law pursuant to K.S.A. 50-636(b). Ex. D, at ¶ 6.3.

C. The 2014 Consent Judgment

314. In 2014, Pfizer paid $35 million to resolve claims by a group of states, including Kansas, relating to Wyeth Pharmaceuticals Inc.'s ("Wyeth") promotional and marketing practices regarding the prescription drug Rapamune®. Pfizer acquired Wyeth five years before the Consent Judgment. Pfizer signed the Consent Judgment on behalf of itself and Wyeth. Final Consent Judgment, *State of Kansas, ex rel. Derek Schmidt. v. Wyeth Pharmaceuticals Inc.*, No. 2014CV777 (Aug. 6, 2014), attached as Exhibit E.

315. According to the 2014 Consent Judgment, "Pfizer shall not make, or cause to be made, any written or oral claim that is false, misleading, or deceptive regarding any Pfizer Product." *Id.* at ¶ 3.1.

316. The 2014 Consent Judgment defined "Pfizer Product" to mean "any FDA-approved prescription drug or biological product manufactured, distributed, sold, marketed or Promoted by Pfizer in the United States." *Id.* at ¶ 2.17.

317. While the 2014 Consent Judgment does not define "biological product," the FDA defines "biological product" to include vaccines. FDA, *What Are "Biologics" Questions and Answers*, content current as of Feb. 6, 2018;[136] *see also* 42 U.S.C. § 262.

318. Under the 2014 Consent Judgment, Pfizer's COVID-19 vaccine is a biological product manufactured, distributed, sold, marketed or Promoted in the United States.

319. Pfizer's COVID-19 vaccine received FDA approval beginning on December 11, 2020.

320. As set forth in the 2014 Consent Judgment, *id.* at ¶ 6.1, the Kansas Attorney General provided Pfizer notice of his reasonable belief that Pfizer has engaged in practices that violate the 2014 Consent Judgment. *See* Ex. B.

321. In response to the notice from Plaintiff Kansas Attorney General, Pfizer did not address all of the issues identified by Plaintiff, did not respond to evidence cited by Plaintiff, and did not produce documents requested by Plaintiff. *See* Ex. C.

322. The 2014 Consent Judgment empowers the Kansas Attorney General to assert any claim that Pfizer has violated this Judgment in a separate civil action and to enforce compliance with the Consent Judgment and to seek any other relief afforded by law, pursuant to K.S.A. 50-636(b). Ex. E, at ¶ 6.3.

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[136] *Available at* https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers.

COUNT I
KANSAS CONSUMER PROTECTION ACT
Violation of the 2008 Consent Judgment, K.S.A. 50-636(b)
(False, misleading, and deceptive claims)

323. All preceding paragraphs are incorporated by reference herein.

324. Pfizer made written and oral claims that were false, misleading and deceptive regarding its COVID-19 vaccine, including but not limited to: Pfizer's COVID-19 vaccine was safe, effective, and prevented transmission of the virus.

325. Pfizer's false, misleading and deceptive claims regarding its COVID-19 vaccine violated the 2008 Consent Judgment, for which the Court should assess an enhanced civil penalty of not more than twenty thousand dollars ($20,000.00) per violation, pursuant to K.S.A. 50-636(b).

326. The State of Kansas has been harmed by Pfizer's breach of provisions in the 2008 Consent Judgment.

COUNT II
KANSAS CONSUMER PROTECTION ACT
Violation of the 2008 Consent Judgment, K.S.A. 50-636(b)
(Clinical studies communications)

327. All preceding paragraphs are incorporated by reference herein.

328. Pfizer made public statements that were published and broadcast through media relating to its COVID-19 vaccine that did not accurately reflect the methodology used to conduct the clinical study, presented favorable information or conclusions from a study that was inadequate in design, scope, or conduct to furnish significant support for such information or conclusions, and/or used statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies

the design or protocol of which are not amenable to formal statistical evaluation, including but not limited to:

a. Statements about Pfizer's original COVID-19 clinical trial on healthy individuals;

b. Statements about Pfizer's COVID-19 trial on pregnant women; and

c. Statements about Pfizer's COVID-19 vaccine booster trial on individuals 65 years old and older.

329. Pfizer also made public statements that were published and broadcast through media relating to its COVID-19 vaccine that presented information from a study in a way that implied that the study represents larger or more general experience with the drug than it actually did, and/or used statistics on numbers of patients, or counts of favorable results or side effects derived from pooling data from various insignificant or dissimilar studies in a way that suggests either that such statistics are valid if they are not or that they are derived from large or significant studies supporting favorable conclusions when such is not the case, including but not limited to:

a. Statements about Pfizer's original COVID-19 clinical trial on healthy individuals;

b. Statements about Pfizer's COVID-19 trial on pregnant women; and

c. Statements about Pfizer's COVID-19 vaccine booster trial on individuals 65 years old and older.

330. Pfizer's public statements about its COVID-19 vaccine that referenced or relied on clinical studies violated the 2008 Consent Judgment, for which the Court should assess an enhanced civil penalty of not more than twenty thousand dollars ($20,000.00) per violation, pursuant to K.S.A. 50-636(b).

331. The State of Kansas has been harmed by Pfizer's breach of provisions in the 2008 Consent Judgment.

COUNT III
KANSAS CONSUMER PROTECTION ACT
Violation of the 2012 Consent Judgment, K.S.A. 50-636(b)
(False, misleading, and deceptive claims)

332. All preceding paragraphs are incorporated by reference herein.

333. Pfizer made, or caused to be made, written and oral claims that were false, misleading, and deceptive regarding its COVID-19 vaccine, including but not limited to: Pfizer's COVID-19 vaccine was safe, effective, and prevented transmission of the virus.

334. Pfizer's false, misleading, and deceptive claims regarding its COVID-19 vaccine violated the 2012 Consent Judgment, for which the Court should assess an enhanced civil penalty of not more than twenty thousand dollars ($20,000.00) per violation, pursuant to K.S.A. 50-636(b).

335. The State of Kansas has been harmed by Pfizer's breach of provisions in the 2012 Consent Judgment.

COUNT IV
KANSAS CONSUMER PROTECTION ACT
Violation of the 2014 Consent Judgment, K.S.A. 50-636(b)
(False, misleading, and deceptive claims)

336. All preceding paragraphs are incorporated by reference herein.

337. Pfizer made, or caused to be made, written and oral claims that were false, misleading, and deceptive regarding its COVID-19 vaccine, including but not limited to: Pfizer's COVID-19 vaccine was safe, effective, and prevented transmission of the virus.

338. Pfizer's false, misleading, and deceptive claims regarding its COVID-19 vaccine violated the 2014 Consent Judgment, for which the Court should assess an enhanced civil penalty of not more than twenty thousand dollars ($20,000.00) per violation, pursuant to K.S.A. 50-636(b).

339. The State of Kansas has been harmed by Pfizer's breach of provisions in the 2014 Consent Judgment.

COUNT V
KANSAS CONSUMER PROTECTION ACT
Deceptive Acts or Practices, K.S.A. 50-626(b)(1)(F)

340. All preceding paragraphs are incorporated by reference herein.

341. Beginning in 2020, Pfizer made representations to Kansas consumers knowingly or with reason to know that its COVID-19 vaccine had uses, benefits or characteristics that Pfizer could not rely upon and did not possess a reasonable basis for making such representation, in violation of K.S.A. 50-626(b)(1)(F), including but not limited to: Pfizer's COVID-19 vaccine was safe, effective, and prevented transmission of the virus.

342. Pfizer's representations to consumers are continuing deceptive acts and practices and each day it exists is a separate violation of the KCPA. Civil penalties of not more than ten thousand dollars ($10,000.00) per violation may be imposed, pursuant to K.S.A. 50-636(d).

343. Consumers have been damaged by Pfizer's violation of the Kansas Consumer Protection Act.

COUNT VI
KANSAS CONSUMER PROTECTION ACT
Deceptive Acts or Practices, K.S.A. 50-626(b)(1)(G)

344. All preceding paragraphs are incorporated by reference herein.

345. Beginning in 2020, Pfizer made representations knowingly or with reason to know that the use, benefit or characteristic of its COVID-19 vaccine had not been proven or otherwise substantiated and Pfizer did not rely upon and possess the type and amount of proof or substantiation represented to exist, in violation of K.S.A. 50-626(1)(G), including but not limited to: Pfizer's COVID-19 vaccine was safe, effective, and prevented transmission.

346. Pfizer's representations to consumers are continuing deceptive acts and practices and each day it exists is a separate violation of the KCPA. Civil penalties of not more than ten thousand dollars ($10,000.00) per violation may be imposed, pursuant to K.S.A. 50-636(d).

347. Consumers have been damaged by Pfizer's violation of the Kansas Consumer Protection Act.

COUNT VII
KANSAS CONSUMER PROTECTION ACT
Deceptive Acts or Practices, K.S.A. 50-626(b)(2)

348. All preceding paragraphs are incorporated by reference herein.

349. Beginning in 2020, Pfizer willfully used, in any oral or written representation, of exaggerations, falsehoods, innuendo, or ambiguity as to a material fact, in violation of K.S.A. 50-626(b)(2), including but not limited to: Pfizer's COVID-19 vaccine was safe, effective, and prevented transmission.

350. Pfizer's deceptive acts and practices are continuing and each day it exists is a separate violation of the KCPA. Civil penalties of not more than ten thousand dollars ($10,000.00) per violation may be imposed, pursuant to K.S.A. 50-636(d).

351. Consumers have been damaged by Pfizer's violation of the Kansas Consumer Protection Act.

COUNT VIII
KANSAS CONSUMER PROTECTION ACT
Deceptive Acts or Practices, K.S.A. 50-626(b)(3)

352. All preceding paragraphs are incorporated by reference herein.

353. Beginning in 2020, Pfizer willfully failed to state a material fact or willfully concealed, suppressed, or omitted a material fact in violation of K.S.A. 50-626(b)(3), including but not limited to:

a. Pfizer's COVID-19 vaccine safety data, including from its clinical trials and confidential internal company documents on adverse events, pregnant animals and pregnant women, and safety signals;

b. Pfizer's COVID-19 vaccine's efficacy, including waning effectiveness; and

c. Pfizer's direct efforts to censor truthful information on social media about Pfizer's COVID-19 vaccine.

354. Pfizer's deceptive acts and practices are continuing and each day it exists is a separate violation of the KCPA. Civil penalties of not more than ten thousand dollars ($10,000.00) per violation may be imposed, pursuant to K.S.A. 50-636(d).

355. Consumers have been damaged by Pfizer's violation of the Kansas Consumer Protection Act.

COUNT IX
KANSAS CONSUMER PROTECTION ACT
Unconscionable Acts or Practices, K.S.A. 50-627(b)(6)

356. All preceding paragraphs are incorporated by reference herein.

357. Beginning in 2020, Pfizer knew or had reason to know that it made a misleading statement of opinion on which the consumer was likely to rely to the consumer's detriment in

violation of K.S.A. 50-627(b)(6), including but not limited to: Pfizer's vaccine was safe, effective, and prevented transmission.

358. Pfizer's unconscionable acts or practices are continuing and each day it exists is a separate violation of the KCPA. Civil penalties of not more than ten thousand dollars ($10,000.00) per violation may be imposed, pursuant to K.S.A. 50-636(d).

359. Consumers have been damaged by Pfizer's violation of the Kansas Consumer Protection Act.

COUNT X
Civil Conspiracy

360. All preceding paragraphs are incorporated by reference herein.

361. Upon information and belief, Pfizer conspired with two or more persons from the federal government and third-party businesses and organizations to willfully conceal, suppress, or omit material facts relating to Pfizer's COVID-19 vaccine.

362. Upon information and belief, Pfizer, the Department of Health and Human Services, and members of the Virality Project, including Stanford, had a meeting of the minds no later than December 2020 to willfully conceal, suppress, or omit material facts relating to Pfizer's COVID-19 vaccine.

363. Upon information and belief, Pfizer, the Biotechnology Innovation Organization, and the Public Goods Project had a meeting of the minds no later than July 2020 to willfully conceal, suppress, or omit material facts relating to Pfizer's COVID-19 vaccine.

364. Pfizer and its co-conspirators took actions to willfully conceal, suppress, or omit material facts relating to Pfizer's COVID-19 vaccine in violation of the Kansas Consumer Protection Act, including K.S.A. 50-626(b)(3).

365. Kansans have been damaged as a proximate result of Pfizer's conspiracy.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff State of Kansas respectfully prays that this Court grant them the following relief:

A. Declare that Pfizer's written and oral claims violate the 2008 Consent Judgment;

B. Order Pfizer to pay the State of Kansas enhanced civil penalties of twenty thousand dollars ($20,000.00) for each violation of the 2008 Consent Judgment pursuant to K.S.A. 50-636(b);

C. Declare that Pfizer's written and oral claims violate the 2012 Consent Judgment;

D. Order Pfizer to pay the State of Kansas enhanced civil penalties of twenty thousand dollars ($20,000.00) for each violation of the 2012 Consent Judgment pursuant to K.S.A. 50-636(b);

E. Declare that Pfizer's written and oral claims violate the 2014 Consent Judgment pursuant to K.S.A. 50-636(b);

F. Order Pfizer to pay the State of Kansas enhanced civil penalties of twenty thousand dollars ($20,000.00) for each violation of the 2014 Consent Judgment;

G. Declare, pursuant to K.S.A. 50-632(a)(1), that Pfizer's deceptive or unconscionable acts or practices violate the Kansas Consumer Protection Act, K.S.A. 50-623, *et seq*.;

H. Order Pfizer to pay a civil penalty of ten thousand dollars ($10,000.00) for each violation of the Kansas Consumer Protection Act pursuant to K.S.A. 50-636;

I. Order Pfizer to pay a civil penalty of ten thousand dollars ($10,000.00) for each day Pfizer's act or practice exists pursuant to K.S.A. 50-636(d);

J. Award Plaintiff State of Kansas damages for Pfizer's violations of the Kansas Consumer Protection Act, K.S.A. 50-636(a);

K. Award Plaintiff State of Kansas reasonable expenses and investigation fees pursuant to K.S.A. 50-636(c);

L. Award Plaintiff State of Kansas damages caused by Pfizer's civil conspiracy; and

M. Grant such other and further relief as the Court deems just and proper.

Dated: June 17, 2024

Respectfully submitted,

KRIS W. KOBACH
ATTORNEY GENERAL

/s/ Kaley Schrader
Frances R. Oleen, #17433
Deputy Attorney General
Kaley Schrader, #27700
Assistant Attorney General
Office of the Attorney General
Public Protection Division
120 SW 10th Ave., 2nd Floor
Topeka, Kansas 66612-1597
Tel: 785-296-3751
Fax: 785-291-3699
kaley.schrader@ag.ks.gov

JAMES OTIS LAW GROUP, LLC

/s/ Justin D. Smith
Justin D. Smith, Mo. Bar No. 63253*
William O. Scharf, Mo. Bar No. 66676*
Michael C. Martinich-Sauter, Mo. Bar. No. 66065*
13321 North Outer Forty Road, Suite 300
St. Louis, Missouri 63017
(816) 678-2103
Justin.Smith@james-otis.com

* *pro hac vice* forthcoming

Exhibit A

FILED BY CLERK
KS. DISTRICT COURT
THIRD JUDICIAL DIST.
TOPEKA, KS

2008 OCT 23 P 4: 31

IN THE DISTRICT COURT OF SHAWNEE COUNTY, KANSAS
Div. 9

STATE OF KANSAS, *ex rel.*, **STEVE SIX, Attorney General,** **Plaintiff,** **v.** **PFIZER INC,** **Defendant.**	)	**No.** 08C1576

(Pursuant to K.S.A. Chapter 60)

JOURNAL ENTRY OF CONSENT JUDGMENT

NOW on this 22 day of Oct, 2008, Plaintiff's Journal Entry of Consent Judgment comes before the Court pursuant to K.S.A. 50-623(b). Plaintiff, the State of Kansas, *ex rel.* Steve Six, Attorney General, appears by and through Emilie Burdette, Assistant Attorney General. Defendant Pfizer Inc appears by and through Kathleen A. Hardee of Shughart Thomson & Kilroy P.C.

The parties advise the Court that they have stipulated and agreed to the following matters: Steve Six is the duly appointed and acting Attorney General of the State of Kansas. The Attorney General's authority to bring this action is derived from the statutory and common law of the State of Kansas, specifically the Kansas Consumer Protection Act, K.S.A. 50-623 *et seq.* Defendant Pfizer Inc (hereinafter "Pfizer" or "Defendant") is a Delaware corporation that conducts business nationwide, including in the State of Kansas; its principal place of business is 235 E 42ND ST, NEW YORK, NY 10017-5703. Pfizer transacts business in the State of Kansas

by advertising, soliciting, selling, promoting and distributing prescription drugs, including BEXTRA/CELEBREX®, to consumers in the State of Kansas and nationwide.

DEFINITIONS

1.

The following definitions shall be used in construing this Judgment:

a. "Covered Conduct" shall mean Pfizer's promotional and marketing practices regarding the prescription drugs Celebrex® and Bextra®, that were the subject of an investigation by the Signatory Attorneys General under the State Consumer Protection Laws.

b. "Effective Date" shall mean the date by which Pfizer and ninety percent (90%) of the States that comprise the Multistate Working Group have executed the Consent Judgment.

c. "FDA Amendments Act of 2007" (or "FDA Amendments Act" or "the Act") shall mean Public Law No. 110-85, which among other things, creates a federal clinical trial registry and results data bank.

d. "FDA's Guidance for Industry" shall mean documents published by the United States Department of Health and Human Services, Food and Drug Administration (FDA), that represent the FDA's current recommendations on a topic.

e. "Individual States" and "State" shall mean each Signatory Attorney General who is participating in the Multistate Working Group.

f. "Pfizer" shall mean Pfizer Inc and its United States-based affiliates, subsidiaries, predecessors, successors, and assigns.

g. "Multistate Executive Committee" shall mean the Attorneys General and their staffs representing Arizona, California, Florida, Illinois, Massachusetts, New York, Ohio, Oregon, Texas, and Vermont.

h. "Multistate Working Group" ("MSWG") shall mean the Attorneys General and their staffs representing Alaska, Arizona, Arkansas, California, Connecticut, Florida, District of

Columbia, Idaho, Illinois, Iowa, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Vermont, Washington, and Wisconsin.

i. "Off-Label" shall mean related to an indication that was not approved by the FDA at the time of dissemination or relating to information that was not contained in the FDA label.

j. "Prescriber" shall mean any physician, dentist, physician assistant, nurse practitioners, and all others with legal authority to prescribe any Pfizer product, as well as pharmacists, members of Pharmacy &Therapeutics committees and others who potentially have an impact on the prescribing of any Pfizer product.

k. "Parties" shall mean Pfizer and the Individual States.

l. "Product" shall mean any prescription drug or biological product manufactured, distributed, sold, marketed or promoted in the United States in any way.

m. "Signatory Attorney(s) General" shall mean the Attorney General, or his or her designee, of each state in the Multistate Working Group.

n. "State Consumer Protection Laws" shall mean the consumer protection laws under which the Signatory Attorneys General have conducted their investigation.[1]

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[1] The States' consumer protection statutes are: ALASKA - *Unfair Trade Practices and Consumer Protection Act*, AS 45.50.471 *et seq.*; ARIZONA - *Consumer Fraud Act*, A.R.S. § 44-1521 *et seq.*; ARKANSAS - Ark. Code Ann. § 4-88-101 *et seq.*; CALIFORNIA - Bus. & Prof. Code §§ 17200 *et seq.* and 17500 *et seq.*; CONNECTICUT - Conn. Gen. Stat. §§ 42-110a *et seq.*; DISTRICT OF COLUMBIA - *Consumer Protection Procedures Act*, D.C. Code § 28-3901 *et seq.*; FLORIDA - *Deceptive and Unfair Trade Practices Act*, Fla. Stat. Ch. 501.201 *et seq.*; IDAHO - *Consumer Protection Act*, Idaho Code Section § 48-601 *et seq.*; ILLINOIS - *Consumer Fraud and Deceptive Business Practices Act*, 815 ILCS § 505/1 *et seq.* (2006 State Bar Edition); IOWA - *Iowa Consumer Fraud Act*, Iowa Code Section 714.16; KANSAS - *Consumer Protection Act*, K.S.A. 50-623 *et seq.*; KENTUCKY - *Consumer Protection Statute*, KRS 367.110 *et seq.*; MAINE - *Unfair Trade Practices Act*, 5 M.R.S.A. § 207 *et seq.*; MARYLAND -

o. "Celebrex" shall mean celecoxib.

p. "Bextra" shall mean valdecoxib.

COMPLIANCE PROVISIONS

2.

The parties have agreed to resolve the issues raised by the Covered Conduct by entering into this Consent Judgment (hereinafter "Judgment").

(a) Pfizer is entering into this Judgment solely for the purpose of settlement, and nothing contained herein may be taken as or construed to be an admission or concession of any violation of law, rule, or regulation, or of any other matter of fact or law, or of any liability or wrongdoing, all of which Pfizer expressly denies. Pfizer does not admit any violation of the State Consumer Protection Laws set forth in footnote 1, and does not admit any wrongdoing that was or could have been alleged by any Attorney General before the date of the Judgment under those

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Consumer Protection Act, Md. Code Ann., Com. Law § 13-101 *et seq.*; MASSACHUSETTS - *Consumer Protection Act*, M.G.L. c. 93A *et seq.*; MICHIGAN - *Michigan Consumer Protection Act*, MCL 445.901 *et seq.*; MONTANA - Mont. Code Ann. § 30-14-101 *et seq.*; NEBRASKA - *Uniform Deceptive Trade Practices Act*, NRS § 87-301 *et seq.*; NEW JERSEY - *New Jersey Consumer Fraud Act*, 56:8-1 *et seq.*; NEW YORK - General Business Law Article 22-A Sections 349, 350 and Executive Law Section 63 (12); NEW MEXICO - *Unfair Practices Act*, NMSA 1978, § 57-12-1 *et seq.*; NEVADA - *Deceptive Trade Practices Act*, Nevada Revised Statutes 598.0903 *et seq.*; NORTH CAROLINA - *Unfair and Deceptive Trade Practices Act*, N.C. Gen. Stat. § 75-1.1 *et seq.*; NORTH DAKOTA - *Unlawful Sales or Advertising Practices*, N.D. Cent. Code. § 51-15-02 *et seq.*; OHIO - *Consumer Sales Practices Act*, R.C. 1345.01 *et seq.*; OREGON - *Unlawful Trade Practices Act*, ORS 646.605 to 646.656; PENNSYLVANIA - *Unfair Trade Practices and Consumer Protection Law*, 73 P.S. § 201-1 *et seq.*; SOUTH CAROLINA - *Unfair Trade Practices Act*, S.C. CODE. ANN. Sections 39-5-10 *et seq.*; SOUTH DAKOTA - *Deceptive Trade Practices Act*, S.D. Codified Laws § 37-24 *et seq.*; TENNESSEE - *Consumer Protection Act*, Tenn. Code Ann. §§ 47-18-101 *et seq.*; TEXAS - *Deceptive Trade Practices - Consumer Protection Act*, Tex. Bus. and Com. Code § 17.47 *et seq.*; VERMONT - *Consumer Fraud Act*, 9 V.S.A. § 2451 *et seq.*; WASHINGTON - *Unfair Business Practices/Consumer Protection Act*, R.C.W. 19.86 *et seq.*; WISCONSIN - Wis. Stat. § 100.18 *et seq.* (Fraudulent Representations) and Wis. Stat. § 100.182 *et seq.* (Fraudulent Drug Advertising).

laws. No part of this Judgment, including its statements and commitments, shall constitute evidence of any liability, fault, or wrongdoing by Pfizer. This document and its contents are not intended for use by any third party for any purpose, including submission to any court for any purpose.

(b) This Judgment shall not be construed or used as a waiver or limitation of any defense otherwise available to Pfizer in any action, or of Pfizer's right to defend itself from, or make any arguments in, any private individual, regulatory, governmental, or class claims or suits relating to the subject matter or terms of this Judgment. This Judgment is made without trial or adjudication of any issue of fact or law or finding of liability of any kind. Notwithstanding the foregoing, a State may file an action to enforce the terms of this Judgment.

(c) It is the intent of the Parties that this Judgment not be admissible in other cases or binding on Pfizer in any respect other than in connection with the enforcement of this Judgment.

(d) No part of this Judgment shall create a private cause of action or confer any right to any third party for violation of any federal or state statute except that a State may file an action to enforce the terms of this Judgment.

(e) All obligations undertaken by Pfizer in this Judgment shall apply prospectively, except to the extent permitted by the National Library of Medicine, Pfizer shall submit, as soon as practicable, clinical trial results to the clinical trial registry and results data bank created by the FDA Amendments Act for all "applicable clinical trials" (as that term is defined by the Act) of FDA-approved Pfizer Products that were initiated after July 1, 2005.

3.

Pfizer shall register clinical trials and submit results to the registry and results data bank as required by the FDA Amendments Act and any accompanying regulations that may be promulgated pursuant to that Act.

4.

Pfizer shall not make any written or oral claim that is false, misleading or deceptive regarding any FDA-approved Pfizer Product.

5.

Pfizer shall not make any written or oral promotional claims of safety or effectiveness for any FDA-approved Pfizer Product in a manner that violates the Food, Drug and Cosmetic Act, 21 U.S.C. § 301 et seq. ("FDCA"), accompanying regulations, or voluntary agreements with FDA, as interpreted by the FDA in a writing by the Director of the Center for Drug Evaluation at the FDA.

6.

Nothing in this Judgment shall require Pfizer to:

(a) take an action that is prohibited by the FDCA or any regulation promulgated thereunder, or by FDA; or

(b) fail to take an action that is required by the FDCA or any regulation promulgated thereunder, or by FDA. Any written or oral promotional claim subject to this Judgment which is the same, or materially the same, as the language required or agreed to by the Director of Division of Drug Marketing, Advertising and Communication or the Director of the Center for Drug Evaluation and Research or their authorized designees in writing shall not constitute a violation of this Judgment.

7.

Following the initial approval of any Pfizer Product indicated for pain relief, Pfizer shall delay direct to consumer ("DTC") television advertising that relates to such indication, if the Director of the Center for Drug Evaluation and Research at FDA recommends such a delay in

writing to Pfizer. Pfizer's delay shall be for the same period as recommended by the Director of the Center for Drug Evaluation and Research at FDA, but in no event shall the period of delay required by this provision of this Judgment exceed 18 months from approval. Should Pfizer run television DTC advertising contrary to a recommendation from the Director of the Center for Drug Evaluation and Research after the expiration of this 18 month period, Pfizer shall provide written notice to the Multistate Executive Committee 30 days prior to running the subject advertisement and shall also provide a copy of all correspondence with FDA relating to the subject advertisement.

8.

Pfizer agrees to submit all new DTC television advertising campaigns for any Pfizer Product to FDA for pre-review, to wait a reasonable time (not less than 45 days) until Pfizer receives a response from FDA prior to running the advertising campaign, and to modify such advertising consistent with any written comments from FDA, whenever received. Simultaneous with running any new DTC television advertisement for which FDA has not provided Pfizer with a pre-review response addressing the substance of the advertisement within the 45-day waiting period prescribed herein, Pfizer shall provide written notice to the Multistate Executive Committee that Pfizer is running the advertisement and that the FDA has not provided Pfizer with a pre-review response addressing the substance of the advertising within the 45-day waiting period, and also provide a copy of all material submitted to FDA for the review of the subject advertisement.

9.

Pfizer's obligations with respect to Paragraph 7 shall remain in effect for eight years following the Effective Date. Pfizer's obligations with respect to Paragraph 8 shall remain in effect for seven years following the Effective Date. With respect to Paragraph 7, Pfizer shall abide by any such written recommendation so long as the submission of the TV advertising campaign is made within eight years following the Effective Date. With respect to Paragraph 8,

Pfizer shall abide by any such written recommendation so long as the submission of the TV advertising campaign is made within seven years of the Effective Date.

10.

When presenting information in detailing pieces, brochures, booklets, mailing pieces, published journals, magazines, other periodicals and newspapers, and broadcast through media such as radio, television, the Internet, and telephone communications systems, about a Clinical Study that relates to an FDA-approved Pfizer Product, Pfizer shall: (a) accurately reflect the methodology used to conduct the Clinical Study; (b) not present favorable information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions; and (c) not use statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluations.

11.

When presenting information in detailing pieces, brochures, booklets, mailing pieces, published journals, magazines, other periodicals and newspapers, and broadcast through media such as radio, television, the Internet, and telephone communications systems, about a Clinical Study or analysis of Clinical Studies as evidence of an FDA-approved Pfizer Product's safety, Pfizer shall not: (a) present information from a study in a way that implies that the study represents larger or more general experience with the drug than it actually does; or (b) use statistics on numbers of patients, or counts of favorable results or side effects derived from pooling data from various insignificant or dissimilar studies in a way that suggests either that such statistics are valid if they are not or that they are derived from large or significant studies supporting favorable conclusions when such is not the case.

12.

When presenting information in detailing pieces, brochures, booklets, mailing pieces, published journals, magazines, other periodicals and newspapers, and broadcast through media such as radio, television, the Internet, and telephone communications systems, about a Clinical Study or analysis of Clinical Studies as evidence of an FDA-approved Pfizer Product's safety, Pfizer shall not: (a) present favorable information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions; (b) use the concept of statistical significance to support a claim that has not been demonstrated to have clinical significance or validity, or fails to reveal the range of variations around the quoted average results; or (c) use statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluation.

13.

(a) Pfizer shall comply with the ACCME Standards for Commercial Support (a copy of the current version is attached hereto as Appendix 1).

(b) Any person who acts in a promotional capacity for Pfizer with respect to an FDA approved Pfizer Product shall be obligated under his or her contract with Pfizer, as a condition for any future promotional relationship with Pfizer, to disclose to Continuing Medical Education ("CME") participants orally and to the CME provider for inclusion in the written materials the existence, nature and purpose of his or her arrangement with Pfizer when a member of the faculty at a CME program if: (i) the Product the faculty member promoted for Pfizer is in the same therapeutic category as the subject of the CME program, and (ii) the CME program occurs within 12 months of the faculty member performing work for or receiving compensation from Pfizer. Such disclosure shall set forth the type of promotional work engaged in by the faculty member and the name of the therapeutic category with respect to such promotion.

(c) Pfizer shall not provide funding for CME when Pfizer has knowledge at the time the decision to fund the CME is made that a speaker at the CME has also been a promotional speaker in the past 12 months at a Pfizer-sponsored promotional event related to the class of drugs to be discussed in the CME.

14.

Pfizer's obligations with respect to CME shall remain in effect for 9 years following the Effective Date. Pfizer's obligations with respect to Paragraph 13(b) shall only apply to speakers' contracts entered into, amended to extend the contract period, or renewed after the date of this Judgment.

15.

Pfizer shall require all individuals who are named as authors on a Pfizer-sponsored manuscript reporting the results of a Pfizer-sponsored study to fulfill the following conditions: (a) the individual shall have made a substantial contribution to the conception and design, or acquisition of data, or analysis and interpretation of data; (b) the individual shall have been involved in drafting the article or revising it critically for important intellectual content; and (c) the individual shall have final approval rights of the version to be published. When a large, multi-center group has conducted the research, the manuscript shall identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship as set forth in (a), (b), and (c) above.

16.

Pfizer shall not disseminate in a promotional context any patient testimonial relating to a Product that does not clearly and conspicuously disclose what the generally expected performance would be in the depicted circumstances or clearly and conspicuously disclose the limited applicability of the experience described by the patient testimonial to what consumers may generally expect to achieve.

17.

Pfizer shall not market two or more Products in a manner that falsely or misleadingly conflates the various properties of the respective Products.

18.

Pfizer shall not compensate physicians for conducting individual, observational teaching sessions in their offices or in the hospital ("mentorships") in which sales representatives who detail a Product participate.

19.

Pfizer shall instruct investigators of Pfizer sponsored clinical trials regarding a Product to obtain a legally effective informed consent from all study subjects or from the subject's legally authorized representative. If Pfizer provides the investigator (or the investigator's Institutional Review Board) with a model informed consent, Pfizer shall not fail to include (a) a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental; (b) a description of any reasonably foreseeable risks or discomforts to the subject; and (c) for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

20.

Pfizer shall not affirmatively seek the inclusion of a Product in hospital protocols or standing orders unless the Product at issue has been approved by the FDA for the indication for

which it is to be included in the protocol or standing order. Notwithstanding the foregoing, Pfizer may disclose to insurance companies and other third party payors any information regarding the inclusion of a Product in hospital protocols or standing orders even if the Product at issue has not been approved by the FDA for the indication for which it is to be included in the protocol or standing order.

21.

Pfizer shall not award prizes or other incentives to its sales force as rewards for specifically increasing the Off-Label use of a Product.

22.

Pfizer shall not disseminate any information describing any Off-Label use of a Product if such use has been submitted to the FDA for approval and the FDA has either advised Pfizer that it refuses to approve such application or that FDA-identified deficiencies must be resolved before approval can be granted unless Pfizer has first clearly and conspicuously disclosed to the information recipient that FDA had issued such advice regarding such Off-Label use. Pfizer may disclose to any recipient of such information whether the information was presented to the FDA prior to the FDA's issuance of such advice regarding the Off-Label use.

23.

Pfizer shall not disseminate a Medical Information Letter, an unabridged reprint or copy of an article from a Peer Reviewed Journal or a Reference Publication, or written information through a Regional Medical Research Specialist ("RMRS") describing any Off-Label use of a Product in response to an unsolicited request by a prescriber or other health care professional unless (a) the information is about a clinical investigation with respect to the Product and experts qualified by scientific training or experience to evaluate the safety or effectiveness of the Product

would consider the subject of the clinical investigation to be scientifically sound or the information is an unabridged reprint or copy of an article from a Peer Reviewed Journal or a Reference Publication; (b) the information is accompanied by a comprehensive bibliography of publications discussing adequate and well-controlled clinical studies published in a medical journal or medical or scientific text that have been previously published about the use of the Product covered by the information (unless the information is a Peer Reviewed Journal or Reference Publication which already includes such a bibliography); and (c) in cases in which experts qualified by scientific training or experience to evaluate the safety or effectiveness of the Product would consider the conclusion of the information to have been specifically called into question by another article(s) or text(s) that experts qualified by scientific training or experience to evaluate the safety or effectiveness of the Product would consider to be scientifically sound, the information must be disseminated with a representative publication that reaches contrary or different conclusions regarding the Off-Label use.

24.

Pfizer shall not disseminate any reprint or copy of an article from a Peer Reviewed Journal or a Reference Publication describing any Off-Label use of the Product to physician specialties that do not customarily prescribe the Product if these materials combined with detailing, advertising, sampling, or other promotional activities promote Off-Label use of the Product.

25.

In the event that FDA issues a final "Guidance For Industry: Good Reprint Practices For The Distribution Of Medical Journal Articles And Medical Or Scientific Reference Publications On Unapproved New Uses Of Approved Drugs And Approved Or Cleared Medical Devices,"

and a provision of said Guidance materially conflicts with any of the provisions of Paragraphs 22 through 24 of this Judgment, Pfizer may petition the Court for modification of those paragraphs, after providing thirty (30) days' notice to the Attorney General. The parties by stipulation may agree to such a modification, which agreement shall be presented to this Court for consideration provided that the parties may jointly agree to a modification only by a written instrument signed by or on behalf of both Pfizer and the Attorney General. If Pfizer wishes to seek a stipulation for a modification from the State, it shall send a written request for agreement to such modification to the Attorney General at least 30 days prior to filing a motion with the Court for such modification. Within 30 days of receipt from Pfizer of a written request for agreement to modify, the Attorney General shall notify Pfizer in writing if the Attorney General agrees to the requested modification. The Attorney General shall not unreasonably withhold his/her consent to the modification. The parties agree it would be unreasonable to withhold consent to the terms provided in the draft "Guidance For Industry: Good Reprint Practices For The Distribution Of Medical Journal Articles And Medical Or Scientific Reference Publications On Unapproved New Uses Of Approved Drugs And Approved Or Cleared Medical Devices," dated February 15, 2008, and attached hereto as Appendix 2, in the event that all such terms are included in the final Guidance For Industry. In the event that all such terms are not included in the final Guidance for Industry, the parties agree to consider whether any such terms that are included in the final Guidance for Industry should form the basis of a modification of Paragraphs 22 through 24 of this Judgment.

26.

Pfizer shall not disseminate any Medical Information Letter describing any Off-Label use of a Product that makes any false or misleading representation regarding a Product.

27.

Pfizer shall not disseminate samples of a Product with the intent of increasing Off-label prescribing of the Product.

28.

When submitting clinical trials relating to Off-label indications to journals for publication, Pfizer shall disclose to the journal that the FDA has not approved the drug for the indication that was the subject of the clinical trial.

29.

The Pfizer Medical Education Grants Office shall manage all requests for funding related to CME regarding Products. Approval decisions shall be made by the Pfizer Medical Education Grants Office alone, and shall be kept separate from the Sales and Marketing function. Notwithstanding the foregoing, decisions to approve a request for funding made by the Pfizer Medical Education Grants Office may be subject to actual funding approval by Pfizer's Chief Financial Officer or other designated officials.

30.

Pfizer shall not use grants to advantage or promote Products. This provision includes, but is not limited to, the following prohibitions:

(a) Sales and Marketing personnel shall not initiate, coordinate or implement grant applications on behalf of any customer or Prescriber;

(b) Sales and Marketing personnel shall not be involved in selecting grantees or CME-funded speakers; and

(c) Sales and Marketing personnel shall not measure or attempt to track in any way the impact of grants or speaking fees on the participating Prescribers' subsequent prescribing habits, practices or patterns.

31.

Pfizer Sales and Marketing personnel shall not approve grant requests regarding Products, nor attempt to influence the Pfizer Medical Education Grants Office to reward any customers or Prescribers with grants for their prescribing habits, practices or patterns.

32.

By its execution of this Judgment, The State of Kansas releases Pfizer and all of its past and present subsidiaries, affiliates, predecessors and successors (collectively, the "Released Parties") from the following: all civil claims, causes of action, damages, restitution, fines, costs, and penalties on behalf of the State of Kansas under the above-cited consumer protection statutes arising from the Covered Conduct that is the subject of this Judgment.

33.

Notwithstanding any term of this Judgment, specifically reserved and excluded from the Release in Paragraph 32 as to any entity or person, including Released Parties, are any and all of the following:

(a) Any criminal liability that any person or entity, including Released Parties, has or may have to the State of Kansas.

(b) Any civil or administrative liability that any person or entity, including Released Parties, has or may have to the State of Kansas not expressly covered by the release in Paragraph 32 above, including but not limited to any and all of the following claims:

i) State or federal antitrust violations;

ii) Reporting practices, including "best price", "average wholesale price" or "wholesale acquisition cost;"

iii) Medicaid violations, including federal Medicaid drug rebate statute violations, Medicaid fraud or abuse, and/or kickback violations related to any State's Medicaid program; and,

iv) State false claims violations.

(c) Any liability under the State of Kansas's above-cited consumer protection laws which any person or entity, including Released Parties, has or may have to individual consumers or State program payors of said State, and which have not been specifically enumerated as included herein.

34.

Within ten (10) days of the Effective Date of this Judgment, Pfizer shall pay a total amount of sixty million dollars ($60,000,000) to be divided and paid by Pfizer directly to each Signatory Attorney General in an amount to be designated by and in the sole discretion of the Multistate Executive Committee. Said payment shall be used by the States for attorneys' fees and other costs of investigation and litigation, or to be placed in, or applied to, the consumer protection enforcement fund, consumer education, litigation or local consumer aid fund or revolving fund, used to defray the costs of the inquiry leading hereto, or for other uses permitted by state law, at the sole discretion of each Signatory Attorney General.

35.

For the purposes of resolving disputes with respect to compliance with this Judgment, should any of the Signatory Attorneys General have a reasonable basis to believe that Pfizer has engaged in a practice that violates a provision of this Judgment subsequent to the Effective Date of this Judgment, then such Attorney General shall notify Pfizer in writing of the specific objection, identify with particularity the provisions of this Judgment that the practice appears to violate, and give Pfizer thirty (30) days to respond to the notification; provided, however, that a Signatory Attorney General may take any action if the Signatory Attorney General concludes

that, because of the specific practice, a threat to the health or safety of the public requires immediate action.

Upon receipt of written notice, Pfizer shall provide a good-faith written response to the Attorney General notification, containing either a statement explaining why Pfizer believes it is in compliance with the Judgment, or a detailed explanation of how the alleged violation occurred and a statement explaining how Pfizer intends to cure the alleged breach. Nothing in this paragraph shall be interpreted to limit the state's Civil Investigative Demand ("CID") or subpoena authority, to the extent such authority exists under applicable state law, and Pfizer reserves all of its rights with respect to a CID or subpoena issued pursuant to such authority.

36.

Upon giving Pfizer thirty (30) days to respond to the notification described above, the Signatory Attorney General shall also be permitted reasonable access to inspect and copy relevant, non-privileged, non-work product records and documents in the possession, custody or control of Pfizer that relate to Pfizer's compliance with each provision of this Judgment as to which cause that is legally sufficient in the State has been shown. If the Signatory Attorney General makes or requests copies of any documents during the course of that inspection, the Signatory Attorney General will provide a list of those documents to Pfizer.

37.

The State may assert any claim that Pfizer has violated this Judgment in a separate civil action solely to enforce compliance with this Judgment, or to seek any other relief afforded by law, but only after providing Pfizer an opportunity to respond to the notification described in Paragraph 35 above; provided, however, that a Signatory Attorney General may take any action if the Signatory Attorney General concludes that, because of the specific practice, a threat to the health or safety of the public requires immediate action.

38.

This Judgment represents the full and complete terms of the settlement entered into by the parties hereto. In any action undertaken by either the Attorneys General, or any of them, or Pfizer, no prior versions of this Judgment, and no prior versions of any of its terms, that were not entered by the Court in this Judgment, may be introduced for any purpose whatsoever.

IT IS SO STIPULATED:

I. General Provisions

A. This Judgment represents the full and complete terms of the settlement entered into by the Parties hereto. In any action undertaken by the Parties, no prior versions of this Judgment, no prior versions of any of its terms, that were not entered by the Court in this Judgment, may be introduced for any purpose whatsoever.

B. This Court retains jurisdiction of this Judgment and the Parties hereto for the purpose of enforcing and modifying this Judgment and for the purpose of granting such additional relief as may be necessary and appropriate.

C. All Notices under this Judgment shall be provided to Emilie Burdette, Assistant Attorney General, by Overnight Mail at: Office of the Kansas Attorney General. 120 SW 10th Ave., 2nd Floor in Topeka, Kansas 66612.

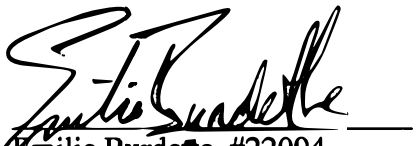
IT IS THEREFORE ORDERED, ADJUDGED AND DECREED that the stipulations and agreements of the parties contained herein are adopted and approved as the findings of fact and conclusions of law of the Court and any monies owed hereunder by Defendant immediately become a judgment upon filing.

IT IS FURTHER ORDERED, ADJUDGED AND DECREED that pursuant to the Kansas Consumer Protection Act, K.S.A. 50-632(b), the Court hereby approves the terms of the Consent Judgment and adopts the same as the order of the Court.

JUDGE

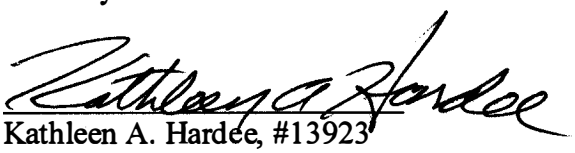
Prepared and approved by:

Attorney for Plaintiff:



Emilie Burdette, #22094
Assistant Attorney General
Office of Kansas Attorney General Steve Six
120 Southwest 10th Ave.. 2nd Floor
Topeka. Kansas 66612
(785) 296-3751
Fax: (785) 291-3699

Attorney for Defendant:



Kathleen A. Hardee, #13923
Shughart Thomson & Kilroy
Twelve Wyandotte Plaza
120 W. 12th Street, Suite 1800
Kansas City, Missouri 64105
(816) 421-3355
Fax: (816) 374-0905

2390149.01

Markus Green
Corporate Counsel
Pfizer Inc

APPENDIX 1

ACCME STANDARDS FOR COMMERCIAL SUPPORT SM

Standards to Ensure the Independence of CME Activities

ACCME

The ACCME Standards for Commercial Support[SM]

Standards to Ensure Independence in CME Activities

STANDARD 1: Independence

1.1 A CME provider must ensure that the following decisions were made free of the control of a commercial interest. (See www.accme.org for a definition of a 'commercial interest' and some exemptions.)

(a) Identification of CME needs;
(b) Determination of educational objectives;
(c) Selection and presentation of content;
(d) Selection of all persons and organizations that will be in a position to control the content of the CME;
(e) Selection of educational methods;
(f) Evaluation of the activity.

1.2 A commercial interest cannot take the role of non-accredited partner in a joint sponsorship relationship.⌘

STANDARD 2: Resolution of Personal Conflicts of Interest

2.1 The provider must be able to show that everyone who is in a position to control the content of an education activity has disclosed all relevant financial relationships with any commercial interest to the provider. The ACCME defines "'relevant' financial relationships" as financial relationships in any amount occurring within the past 12 months that create a conflict of interest.

2.2 An individual who refuses to disclose relevant financial relationships will be disqualified from being a planning committee member, a teacher, or an author of CME, and cannot have control of, or responsibility for, the development, management, presentation or evaluation of the CME activity.

2.3 The provider must have implemented a mechanism to identify and resolve all conflicts of interest prior to the education activity being delivered to learners.⌘

STANDARD 3: Appropriate Use of Commercial Support

3.1 The provider must make all decisions regarding the disposition and disbursement of commercial support.

3.2 A provider cannot be required by a commercial interest to accept advice or services concerning teachers, authors, or participants or other education matters, including content, from a commercial interest as conditions of contributing funds or services.

3.3 All commercial support associated with a CME activity must be given with the full knowledge and approval of the provider.

Written agreement documenting terms of support

3.4 The terms, conditions, and purposes of the commercial support must be documented in a written agreement between the commercial supporter that includes the provider and its educational partner(s). The agreement must include the provider, even if the support is given directly to the provider's educational partner or a joint sponsor.

3.5 The written agreement must specify the commercial interest that is the source of commercial support.

3.6 Both the commercial supporter and the provider must sign the written agreement between the commercial supporter and the provider.

Expenditures for an individual providing CME

3.7 The provider must have written policies and procedures governing honoraria and reimbursement of out-of-pocket expenses for planners, teachers and authors.

3.8 The provider, the joint sponsor, or designated educational partner must pay directly any teacher or author honoraria or reimbursement of out-of–pocket expenses in compliance with the provider's written policies and procedures.

3.9 No other payment shall be given to the director of the activity, planning committee members, teachers or authors, joint sponsor, or any others involved with the supported activity.

3.10 If teachers or authors are listed on the agenda as facilitating or conducting a presentation or session, but participate in the remainder of an educational event as a learner, their expenses can be reimbursed and honoraria can be paid for their teacher or author role only.

Expenditures for learners

3.11 Social events or meals at CME activities cannot compete with or take precedence over the educational events.

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3.12 The provider may not use commercial support to pay for travel, lodging, honoraria, or personal expenses for non-teacher or non-author participants of a CME activity. The provider may use commercial support to pay for travel, lodging, honoraria, or personal expenses for bona fide employees and volunteers of the provider, joint sponsor or educational partner.

Accountability

3.13 The provider must be able to produce accurate documentation detailing the receipt and expenditure of the commercial support. ⌘

STANDARD 4: Appropriate Management of Accompanying Commercial Information

4.1 Arrangements for commercial exhibits or advertisements cannot influence planning or interfere with the presentation, nor can they be a condition of the provision of commercial support for CME activities.

4.2 Product-promotion material or product-specific advertisement of any type is prohibited in or during CME activities. The juxtaposition of editorial and advertising material on the same products or subjects must be avoided. Live (staffed exhibits, presentations) or enduring (printed or electronic advertisements) promotional activities must be kept separate from CME.

- For ***print***, advertisements and promotional materials will not be interleafed within the pages of the CME content. Advertisements and promotional materials may face the first or last pages of printed CME content as long as these materials are not related to the CME content they face **and** are not paid for by the commercial supporters of the CME activity.
- For ***computer based***, advertisements and promotional materials will not be visible on the screen at the same time as the CME content and not interleafed between computer 'windows' or screens of the CME content
- For ***audio and video recording***, advertisements and promotional materials will not be included within the CME. There will be no 'commercial breaks.'
- For ***live, face-to-face CME***, advertisements and promotional materials cannot be displayed or distributed in the educational space immediately before, during, or after a CME activity. Providers cannot allow representatives of Commercial Interests to engage in sales or promotional activities while in the space or place of the CME activity.

4.3 Educational materials that are part of a CME activity, such as slides, abstracts and handouts, cannot contain any advertising, trade name or a product-group message.

4.4 Print or electronic information distributed about the non-CME elements of a CME activity that are not directly related to the transfer of education to the learner, such as schedules and content descriptions, may include product-promotion material or product-specific advertisement.

4.5 A provider cannot use a commercial interest as the agent providing a CME activity to learners, e.g., distribution of self-study CME activities or arranging for electronic access to CME activities. ⌘

STANDARD 5: Content and Format without Commercial Bias

5.1 The content or format of a CME activity or its related materials must promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

5.2 Presentations must give a balanced view of therapeutic options. Use of generic names will contribute to this impartiality. If the CME educational material or content includes trade names, where available trade names from several companies should be used, not just trade names from a single company.⌘

STANDARD 6: Disclosures Relevant to Potential Commercial Bias

Relevant financial relationships of those with control over CME content

6.1 An individual must disclose to learners any relevant financial relationship(s), to include the following information:

- The name of the individual;
- The name of the commercial interest(s);
- The nature of the relationship the person has with each commercial interest.

6.2 For an individual with no relevant financial relationship(s) the learners must be informed that no relevant financial relationship(s) exist.

Commercial support for the CME activity.

6.3 The source of all support from commercial interests must be disclosed to learners. When commercial support is 'in-kind' the nature of the support must be disclosed to learners.

6.4 'Disclosure' must never include the use of a trade name or a product-group message.

Timing of disclosure

6.5 A provider must disclose the above information to learners prior to the beginning of the educational activity. ⌘

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APPENDIX 2

Guidance for Industry:

Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For single copies of this draft guidance, please contact: Office of Policy, Food and Drug Administration, 5600 Fishers Lane, rm. 14-101, HF-11, Rockville, MD 20857, (301) 827-3360.

For questions regarding this draft document, contact Jarilyn Dupont, Office of Policy, Food and Drug Administration, (301) 827-3360.

U.S. Department of Health and Human Services
Food and Drug Administration

February 2008

Contains Nonbinding Recommendations
Draft – Not for Implementation

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Contains Nonbinding Recommendations
Draft – Not for Implementation

Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices

This draft guidance document represents the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You may use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, please contact the appropriate FDA staff.

I. Introduction

This draft guidance is intended to describe the Food and Drug Administration's (FDA or Agency) current thinking regarding "Good Reprint Practices" with regard to the distribution of medical journal articles and scientific or medical reference publications (referred to generally as medical and scientific information) that discuss unapproved new uses for approved drugs[1] or approved or cleared medical devices marketed in the United States to healthcare professionals and healthcare entities.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable rights or responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Section 401 of the Food and Drug Administration Modernization Act (FDAMA (21 U.S.C. § 360aaa, § 551, Federal Food, Drug, and Cosmetic Act (FD&C Act))), described certain conditions under which a drug or medical device manufacturer[2] could choose to disseminate medical and scientific information discussing unapproved uses of approved drugs and cleared or approved medical devices to healthcare professionals and certain entities (including pharmacy benefits managers, health insurance issuers, group health plans, and Federal or State governmental agencies). FDAMA section 401 provided that, if these conditions were met, dissemination of such journal articles or reference publications would not be considered as evidence of the manufacturer's intent that the product be used for an unapproved new use. FDA implementing regulations were codified at 21 C.F.R. Part 99.

In 2000, subsequent to a decision by the United States Court of Appeals for the District of Columbia Circuit, FDA published a Notice (65 Fed. Reg. 14286, March 16, 2000) clarifying the applicability of the FDAMA section 401 provision and the FDA implementing regulations. In that Notice, FDA stated that the statute and implementing regulations constituted a "safe harbor" for a manufacturer that complies with them before and while disseminating journal articles and reference publications about "new uses" of approved or cleared products. If a manufacturer complied with the FDAMA provision, the distribution of such journal articles or reference publications would not be used as evidence of an intent that the product distributed by the manufacturer be used for an unapproved use. The Notice stated that if a manufacturer chose to disseminate materials but not proceed under FDAMA section 401, that failure would not constitute an independent violation of law.

FDAMA section 401 ceased to be effective on September 30, 2006, and the implementing regulations are no longer applicable. In light of the statute's sunset, FDA is providing its current views on the dissemination of medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities.

III. Purpose

As explained in FDA's March 16, 2000 Notice, the FD&C Act and FDA's implementing regulations generally prohibit manufacturers of new drugs or medical devices from distributing products in interstate commerce for any intended use that FDA has not approved as safe and effective or cleared through a substantial equivalence determination. (E.g., FD&C Act §§ 505(a), 502(o), 501(f)(1)(B), 301(a) and (d); 21 U.S.C. §§ 355, 352(o), 351(f)(1)(B), 331(a) and (d)). An approved new drug that is marketed for an unapproved use becomes misbranded and an unapproved new drug with respect to that use. Similarly, a medical device that is promoted for a use that has not been approved or cleared by FDA is adulterated and misbranded.

FDA does, however, recognize the important public policy reasons for allowing manufacturers to disseminate truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities. Once a drug or medical device has been approved or cleared by FDA, generally healthcare professionals may lawfully use or prescribe that product for uses or treatment regimens that are not included in the product's approved labeling (or, in the case of a medical device cleared under the 510(k) process, in the product's statement of intended uses). These off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals' receipt of medical journal articles and medical or scientific reference publications on unapproved or new uses of approved or cleared medical products that are truthful and not misleading.

FDA's legal authority to determine whether distribution of medical or scientific information constitutes promotion of an unapproved "new use," or whether such activities cause a product to be misbranded or adulterated has not changed. In recognition of the public health value to healthcare professionals of receiving truthful and non-misleading scientific and medical information, FDA is providing recommendations concerning "Good Reprint Practices" for the dissemination of medical journal articles and medical or scientific reference publications on unapproved uses of drugs and medical devices.[3]

IV. Agency Recommendations for Good Reprint Practices

Scientific and medical information that concerns the safety or effectiveness of an approved drug or approved or cleared medical device for a new use that is not included in the product's approved labeling or statement of intended uses (including unapproved or new uses of approved drugs and approved or cleared devices) is often published in journal articles or reference publications. These publications are often distributed by manufacturers to healthcare professionals or healthcare entities. When a manufacturer disseminates such medical and scientific information, FDA recommends that the following principles of "Good Reprint Practices" be followed.

A. Types of Reprints/Articles/Reference Publications

A scientific or medical journal article that is distributed should:

- be published by an organization that has an editorial board that uses experts who have demonstrated expertise in the subject of the article under review by the organization and who are independent of the organization to review and objectively select, reject, or provide comments about proposed articles, and that has a publicly stated policy, to which the organization adheres, of full disclosure of any conflict of interest or biases for all authors, contributors, or editors associated with the journal or organization;
- be peer-reviewed and published in accordance with the peer-review procedures of the organization; and
- not be in the form of a special supplement or publication that has been funded in whole or in part by one or more of the manufacturers of the product that is the subject of the article.

A scientific or medical reference publication that is distributed should not be:

- primarily distributed by a drug or device manufacturer, but should be generally available in bookstores or other independent distribution channels where medical textbooks are sold;
- written, edited, excerpted, or published specifically for, or at the request of, a drug or device manufacturer; or
- edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer.

The information contained in the above scientific or medical journal article or reference publications should address adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device[4]. The information must not:

- be false or misleading, such as a journal article or reference text that is inconsistent with the weight of credible evidence derived from adequate and well-controlled clinical investigations (e.g., where a significant number of other studies contradict the article or reference text's conclusions), that has been withdrawn by the journal or disclaimed by the author, or that discusses a clinical investigation where FDA has previously informed the company that the clinical investigation is not adequate and well-controlled; or
- pose a significant risk to the public health.

The following publications are examples of publications that would not be considered consistent with the Good Reprint Practices outlined in this draft guidance:

- letters to the editor;
- abstracts of a publication;
- reports of Phase 1 trials in healthy subjects; or
- reference publications that contain little or no substantive discussion of the relevant investigation or data.

B. Manner in which to Disseminate Scientific and Medical Information

Scientific or medical information that is distributed should:

- be in the form of an unabridged reprint, copy of an article, or reference publication;
- not be marked, highlighted, summarized, or characterized by the manufacturer in any way;
- be accompanied by the approved labeling for the drug or medical device;
- be accompanied by a comprehensive bibliography of publications discussing adequate and well-controlled clinical studies published in a medical journal or medical or scientific text that have been previously published about the use of the drug or medical device covered by the information disseminated (unless the information already includes such a bibliography);
- in cases where the conclusions of article or text to be disseminated have been specifically called into question by another article(s) or text(s), be disseminated with a representative publication that reaches contrary or different conclusions regarding the unapproved use; and

- be distributed separately from information that is promotional in nature. For example, if a sales representative delivers a reprint to a physician in his office, the reprint should not be physically attached to any promotional material the sales representative uses or delivers during the office visit and should not be the subject of discussion between the sales representative and the physician during the sales visit.[5] Similarly, while reprints may be distributed at medical or scientific conferences in settings appropriate for scientific exchange, reprints should not be distributed in promotional exhibit halls or during promotional speakers' programs.

The journal reprint or reference publication should be accompanied by a prominently displayed and permanently affixed statement disclosing:

- that the uses described in the information have not been approved or cleared by FDA, as applicable to the described drug or medical device;
- the manufacturer's interest in the drug or medical device that is the subject of the journal reprint or reference text;
- any author known to the manufacturer as having a financial interest in the product or manufacturer or receiving compensation from the manufacturer, if applicable;
- any person known to the manufacturer who has provided funding for the study, if applicable; and
- any significant risks or safety concerns known to the manufacturer concerning the unapproved use that are not discussed in the journal article or reference text.

V. Summary

FDA recognizes that the public health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses of approved or cleared medical products. Accordingly, if a manufacturer follows the recommendations described in Section IV of this draft guidance and there is no unlawful promotion of the product, FDA does not intend to use the distribution of such medical and scientific information as evidence of an intent by the manufacturer that the product be used for an unapproved use.[6]

Footnotes

[1] As used in this draft guidance, the term "drug" includes biological products licensed under Section 351(a) of the Public Health Service Act. See 42 U.S.C. § 262(j).

[2] As used in this draft guidance, the term "manufacturer" means a person who manufactures a drug or device or who is licensed by such person to distribute or market the drug or device. The term may also include the sponsor of the approved, licensed, or cleared drug or device.

[3] This draft guidance does not apply to scientific or medical information distributed in response to unsolicited requests for scientific or medical information from health care professionals. See 59 Fed. Reg. 59820, 59823 (November 18, 1994).

[4] In the case of medical devices, journal articles or reference publications discussing significant non-clinical research may be consistent with this draft guidance.

[5] To the extent that the recipients of such information have questions, the Agency recommends that the sales representative refer such questions to a medical/scientific officer or department, and that the officer or department to which the referral is made be separate from the sales and/or marketing departments.

[6] Given the sunset of FDAMA § 401, the other elements that comprised § 401 which are not specifically described in this draft guidance are no longer applicable.

For More Information

Press Release *(February 15, 2008)*
Federal Register (Docket No. FDA-2008-D-0053, OC 2007268)

Exhibit B

STATE OF KANSAS
OFFICE OF THE ATTORNEY GENERAL

KRIS W. KOBACH
ATTORNEY GENERAL

MEMORIAL HALL
120 SW 10TH AVE., 2ND FLOOR
TOPEKA, KS 66612-1597
(785) 296-2215 • FAX (785) 296-6296
WWW.AG.KS.GOV

April 22, 2024

Pfizer Inc.
c/o Milton Marquis
1200 19th Street, NW
3rd Floor
Washington, D.C. 20036
mmarquis@cozen.com

SENT BY ELECTRONIC MAIL

RE: Notice of Consent Judgment Violations

Dear Pfizer and Pfizer representatives:

This notice is provided pursuant to Paragraph 35 of the Final Consent Judgment in *State of Kansas, ex rel. Steve Six v. Pfizer Inc.*, No. 08CV1576 (Oct. 23, 2008) ("Celebrex Consent Judgment"); Paragraph 6.1 of the Final Consent Judgment in *State of Kansas, ex rel. Derek Schmidt v. Pfizer Inc.*, No. 12CV1339 (Dec. 13, 2012); ("Lyrica Consent Judgment"); and Paragraph 6.1 of the Final Consent Judgment in *State of Kansas, ex rel. Derek Schmidt. v. Wyeth Pharmaceuticals Inc.*, No. 2014CV777 (Aug. 6, 2014). Pursuant to the terms in these consent judgments, please provide a good-faith written response to this notice within 30 days.

I. False, misleading, or deceptive written or oral claims

All three consent judgments prohibit false, misleading, or deceptive claims regarding Pfizer products. Celebrex Consent Judgment, ¶ 4; Lyrica Consent Judgment, ¶ 3.1; Rapamune Consent Judgment, ¶ 3.1. The consent judgments broadly cover any Pfizer "prescription drug or biological product manufactured, distributed, sold, marketed or promoted by Pfizer in the United States." Celebrex Consent Judgment, ¶ 1(l); Lyrica Consent Judgment, ¶ 2.18; Rapamune Consent Judgment, ¶ 2.17. The consent judgments do not limit these prohibitions on false, misleading, or deceptive claims by time or by specific Pfizer product.

These broad provisions apply to claims Pfizer made or that it caused to be made about its COVID-19 vaccine. Federal law defines "biological product" to include vaccines. 42 U.S.C. § 262(i)(1); *see also* 21 U.S.C. § 360bbb-3(a)(4)(A). Pfizer manufactured, distributed, sold,

marketed, and promoted its COVID-19 vaccine in the United States, including in Kansas.

A. False, Misleading, or Deceptive Safety Claims

Pfizer appears to have made, or caused to be made, numerous claims about its COVID-19 vaccine's safety that are false, misleading, or deceptive. The examples provided below are illustrative and are not intended to be an exhaustive list of all safety statements.

1. "No serious safety concerns." On April 1, 2021, Pfizer issued a press release confirming "no serious safety concerns through up to six months following second dose" of the Pfizer COVID-19 vaccine.[1] However, as of February 28, 2021, Pfizer had received more than 42,000 case reports containing more than 158,000 adverse events from its COVID-19 vaccine, including injuries, adverse pregnancy outcomes, and fatalities.[2] In addition, at the time of its press release, Pfizer knew the results of a June 29, 2020 to October 12, 2020 lab rat study. In that study, pregnant rats receiving variations of Pfizer's COVID-19 vaccine had the following effects at a higher rate than the control group rats:
    a. lost their entire litters;
    b. delivered stillborn offspring;
    c. pre-implantation loss (twice as high as the control group);
    d. pre-birth loss (almost twice as high as the control group);
    e. delivered fewer offspring;
    f. had lower body weight;
    g. consumed less food;
    h. had multiple fetuses with severe soft tissue anomalies;
    i. had multiple fetuses with skeletal anomalies;
    j. had a smaller mean live litter size.[3]

2. "Effective and safe." On August 23, 2021, Pfizer CEO Dr. Bourla said that the Pfizer vaccine "is effective and safe."[4] Similarly, on September 16, 2021, Pfizer CEO Dr. Bourla said, "We have been very successful in developing an effective and safe vaccine."[5] Yet according to an internal Pfizer document, "[s]ince April 2021, increased cases of

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[1] *Pfizer and BioNTech Confirm High Efficacy and No Serious Safety Concerns Through Up to Six Months Following Second Dose in Updated Topline Analysis of Landmark COVID-19 Vaccine Study*, Pfizer (Apr. 1, 2021), *at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious.

[2] Worldwide Safety and Pfizer, *5.3.6 Cumulative Analysis of Post-Authorization Adverse Event Reports of PF-07302048 (BNT162B2) Received Through 28-Feb-2021*, approved Apr. 30, 2021, 6, *at* https://phmpt.org/wp-content/uploads/2022/04/reissue_5.3.6-postmarketing-experience.pdf.

[3] Charles River, "A Combined Fertility and Development Study (Including Teratogenicity and Postnatal Investigations) of BNT162b1, BNT162b2 and BNT162b3 by Intramuscular Administration in the Wistar Rat," approved Dec. 22, 2020, at 13, *at* https://pdata0916.s3.us-east-2.amazonaws.com/pdocs/110122/125742_S1_M4_20256434.pdf.

[4] Antonio Planas, *'Effective and safe': Pfizer CEO says FDA's full approval should result in more vaccinations*, NBC NEWS (Aug. 23, 2021), *at* https://www.nbcnews.com/news/us-news/effective-safe-pfizer-ceo-says-fda-s-full-approval-should-n1277478.

[5] *Continuing to Follow the Science: An Open Letter from Pfizer Chairman and CEO Dr. Albert Bourla*, Pfizer (Sept. 16, 2021), *at* https://www.pfizer.com/news/announcements/continuing-follow-science-open-letter-pfizer-chairman-and-ceo-dr-albert-bourla.

myocarditis and pericarditis have been reported in the United States after mRNA COVID-19 vaccination (Pfizer-BioNTech and Moderna), particularly in adolescents and young adults (CDC 2021)."[6] After the CDC had received 1,200 reports of heart inflammation relating to the COVID-19 vaccine, in June 2021, the FDA added a warning about the risk of myocarditis and pericarditis to the Pfizer COVID-19 vaccine fact sheet.[7]

3. "Not a single safety signal." On January 18, 2023, in response to questions about stroke and myocarditis concerns related to the Pfizer vaccine, Pfizer CEO Dr. Bourla said, "We constantly review and analyze the data. We've seen not a single [safety] signal although we have distributed billions of doses."[8] At the time Dr. Bourla made his statement, the CDC website contained the following statement: "In April 2021, increased cases of myocarditis and pericarditis were reported in the United States after mRNA COVID-19 vaccination (Pfizer-BioNTech and Moderna). Data from multiple studies show a rare risk for myocarditis and/or pericarditis following receipt of mRNA COVID-19 vaccines. These rare cases of myocarditis or pericarditis have occurred most frequently in adolescent and young adult males, ages 16 years and older, within 7 days after receiving the second dose of an mRNA COVID-19 vaccine (Pfizer-BioNTech and Moderna). There has not been a similar reporting pattern observed after receipt of the Janssen COVID-19 Vaccine (Johnson & Johnson)."[9] In addition, days before Pfizer's January 2023 claim, the CDC's and FDA's "surveillance system flagged a possible link between the new Pfizer-BioNTech bivalent Covid-19 vaccine and strokes in people aged 65 and over, . . ."[10] Finally, at least by May 2021, government studies had connected the Pfizer vaccine to fatalities: "[a]mong 100 reported deaths, a causal link to the vaccine was considered probable in 10 cases, possible in 26, and unlikely in 59. Five were unclassifiable."[11]

Based on the contradictions between Pfizer's public statements and internal reports, Pfizer appears to have made false, misleading, or deceptive claims about its COVID-19 vaccine's safety in violation of its consent judgments with the State of Kansas.

Under the consent judgments, during Pfizer's time to respond to this notice, the Kansas Attorney General "shall also be permitted reasonable access to inspect and copy relevant, non-

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[6] Pfizer, *Myocarditis/Pericarditis After mRNA COVID-19 Vaccine Administration: Potential Mechanisms and Recommended Future Actions*, Feb. 11, 2022, at 18, *at* https://downloads.ctfassets.net/syq3snmxclc9/7AqXvmHTBMFOxeGxwMBxxS/7d21477d2697da8adf980ccce52b983f/3-16-23_-_Pfizer_Docs_Watermarked.pdf.

[7] Lauren Mascarenhas, *FDA adds a warning to Covid-19 vaccines about risk of heart inflammation*, CNN, June 26, 2021, *at* https://www.cnn.com/2021/06/25/health/fda-covid-vaccine-heart-warning/index.html.

[8] *Pfizer CEO Albert Bourla discusses new vaccines in the pipeline*, CNBC, Jan. 18, 2023, 3:18 *at* https://www.cnbc.com/video/2023/01/18/pfizer-ceo-albert-bourla-discusses-new-vaccines-to-be-released.html.

[9] CDC, *Clinical Considerations: Myocarditis and Pericarditis after Receipt of mRNA COVID-19 Vaccines Among Adolescents and Young Adults*, archived from January 18, 2023, *at* https://web.archive.org/web/20230118015839/https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html.

[10] Ben Leonard and Lauren Gardner, *CDC, FDA see possible link between Pfizer's bivalent shot and strokes*, Politico, Jan. 13, 2023, *at* https://www.politico.com/news/2023/01/13/cdc-fda-pfizer-bivalent-vaccine-possible-strokes-00077933.

[11] Wyller TB, Kittang BR, Ranhoff AH, Harg P, Myrstad M. Nursing home deaths after COVID-19 vaccination. *Tidsskr Nor Legeforen* 2021;141. doi:10.4045/tidsskr.21.0383. https://tidsskriftet.no/en/2021/05/originalartikkel/nursing-home-deaths-after-covid-19-vaccination.

privileged, non-work product records and documents in the possession, custody or control of Pfizer that relate to Pfizer's compliance with each provision" of the consent judgments. Celebrex Consent Judgment, ¶ 36; Lyrica Consent Judgment, ¶ 6.2; Rapamune Consent Judgment, ¶ 6.2. In addition to the review provided by these consent judgments, the Kansas Attorney General has the right to request these records under Kansas law. K.S.A. 50-631.

Pursuant to the authority provided by the consent judgments and Kansas law, please provide, or make available for inspection and copying, the following documents within 30 days, by May 23, 2024:

1. All emails to or from Pfizer's communications team relating to the April 1, 2021 press release before the press release was issued.

2. All emails between Pfizer personnel and the CDC or FDA relating to Pfizer's "5.3.6 Cumulative Analysis of Post-Authorization Adverse Event Reports of PF-07302048 (BNT162B2) Received Through 28-Feb-2021."

3. All emails received by Pfizer personnel from a CDC or FDA email address between December 1, 2020 and October 1, 2021 containing "myocarditis" or "pericarditis."

4. All emails Pfizer personnel sent in 2021 or 2022 to a CDC or FDA email address containing the words "safety signal" or "safety signals."

Requests #2, #3, and #4 are intended to encompass emails between those Pfizer personnel and CDC and/or FDA personnel communicating about Pfizer's COVID-19 vaccine, and not emails sent or received by rank-and-file Pfizer employees that contain search terms.

B. False, Misleading, or Deceptive Efficacy Claims

Pfizer appears to have made, or caused to be made, numerous claims about its COVID-19 vaccine's efficacy that are false, misleading, or deceptive. The examples provided below are illustrative and are not intended to be an exhaustive list of all efficacy statements.

1. "Prevent." On November 9, 2020, when Pfizer issued a press release to promote its vaccine Phase 3 trial results, Pfizer CEO Dr. Bourla said, "The first set of results from our Phase 3 COVID-19 vaccine trial provides the initial evidence of our vaccine's ability to prevent COVID-19."[12] Dr. Bourla further claimed, "With today's news, we are a significant step closer to providing people around the world with a much-needed breakthrough to help bring an end to this global health crisis."[13] However, as the FDA found when it reviewed Pfizer's results, "[a]s the interim and the final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months."[14] The

[12] *Pfizer and BioNTech Announce Vaccine Candidate Against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study*, Pfizer, Nov. 9, 2020, *at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against.
[13] *Id.*
[14] FDA, Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum, Dec. 11, 2020, 49, *at* https://www.fda.gov/media/144416/download.

FDA also found that "[a]dditional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection."[15]

2. "Highly effective with 91.3% vaccine efficacy." On April 1, 2021, Pfizer issued a press release that celebrated "high efficacy" in Pfizer's COVID-19 vaccine through up to six months after the second dose.[16] Pfizer represented that "[a]nalysis of 927 confirmed symptomatic cases of COVID-19 demonstrates BNT162b2 is highly effective with 91.3% vaccine efficacy observed against COVID-19, measured seven days through up to six months after the second dose."[17] However, at that time, Pfizer possessed data showing that more than four months after the second dose of Pfizer's COVID-19 vaccine, the efficacy rate was 83.7%.[18] Blood samples collected six months after the second dose indicated that effectiveness continued to wane.[19] Pfizer did not publicly disclose that effectiveness waned to 83.7% until July 28, 2021, in a Pfizer preprint study.[20]

3. Variants. On February 25, 2021, Pfizer CEO Dr. Bourla said data suggested that individuals fully vaccinated with Pfizer's COVID-19 were protected against any variant currently known, including the South African, Brazilian, and UK variants.[21] Pfizer's chief medical officer said in October 2021, "[o]ur variant-specific analysis clearly shows that the BNT162b2 vaccine is effective against all current variants of concern, including delta."[22] In fact, Pfizer's COVID-19 vaccine was ineffective against variants. For example, government officials and researchers found that Pfizer's COVID-19 vaccine was just 53% to 64% effective against the Delta variant.[23]

Based on the contradictions between Pfizer's public statements and internal reports, it appears that Pfizer made false, misleading, or deceptive claims about its COVID-19 vaccine's efficacy in violation of its consent judgments with the State of Kansas.

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[15] *Id.* at 51.
[16] *Pfizer and BioNTech Confirm High Efficacy and No Serious Safety Concerns Through Up to Six Months Following Second Dose in Updated Topline Analysis of Landmark COVID-19 Vaccine Study*, Pfizer, Apr. 1, 2021, *at* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious.
[17] *Id.*
[18] *2.7.3 Summary of Clinical Efficacy*, approved on Apr. 30, 2021, at 38, *at* https://clinical-information.canada.ca/ci-rc-vu.pdf?file=m2/27-clin-sum/summary-clin-efficacy-covid19-1.pdf&id=252736.
[19] *Id.* at 169, 171.
[20] Alexa Lardieri, *Pfizer Vaccine Protection Declines After Six Months, Boosters Protect Against Delta Variant*, U.S. NEWS & WORLD REPORT, July 28, 2021, *at* https://www.usnews.com/news/health-news/articles/2021-07-28/pfizer-vaccine-protection-declines-after-six-months-boosters-protect-against-delta-variant.
[21] *Exclusive interview with Pfizer CEO Albert Bourla*, NBC News (Feb. 25, 2021), at 0:15 *at* https://www.nbcnews.com/nightly-news/video/exclusive-interview-with-pfizer-ceo-albert-bourla-101605957789.
[22] Berkeley Lovelace Jr., *Pfizer Covid shot protects people form hospitalization even as effectiveness against infection falls, Lancet study confirms*, CNBC (Oct. 4, 2021), *at* https://www.cnbc.com/2021/10/04/pfizer-covid-vaccine-protection-against-infection-tumbles-to-47percent-study-confirms.html.
[23] *Id.*; Dov Lieber, *Pfizer Vaccine Less Effective Against Delta Infections but Prevents Severe Illness, Israeli Data Show*, THE WALL STREET JOURNAL (July 6, 2021), *at* https://www.wsj.com/articles/pfizers-covid-19-vaccine-is-less-effective-against-delta-variant-israeli-data-show-11625572796.

Pursuant to the authority provided by consent judgments and Kansas law,[24] please provide, or make available for inspection and copying, the following documents within 30 days, by May 23, 2024:

1. All emails to or from Pfizer's communications team relating to the July 28, 2021 preprint study before the study was released.

2. All emails between Pfizer personnel and the CDC or FDA relating to Pfizer's "2.7.3 Summary of Clinical Efficacy."

3. All data Pfizer CEO Dr. Bourla relied on for his February 25, 2021 statement that Pfizer's COVID-19 vaccine protected against any variant currently known.

C. False, Misleading, or Deceptive Transmission Claims

Pfizer appears to have made, or caused to be made, numerous claims about its COVID-19 vaccine's effect on transmission that are false, misleading, or deceptive. The examples provided below are illustrative and are not intended to be an exhaustive list of all efficacy statements.

Pfizer CEO Dr. Bourla repeatedly represented to the American people that Pfizer's COVID-19 vaccine prevented transmission because the lives of loved ones were in jeopardy without it.

- Pfizer's CEO Dr. Bourla told the American people on December 14, 2020, that not receiving a COVID-19 vaccine would affect the lives of those around them: "[T]his choice not to vaccinate will not affect only your health or your life. Unfortunately, it will affect the lives of others and likely the lives of the people you love the most, who are the people that usually you are in contact with. So, I think, trust science."[25]

- In January 2021, Pfizer CEO Dr. Bourla repeated his warning to Americans that not receiving a COVID-19 vaccine would affect the lives of those around them: "What I would say to people who fear the vaccine is that they need to recognize that the decision to take it or not will not affect only their own lives. It will affect the lives of others. And most likely it will affect the lives of people that they love the most, who are the people that they socialize the most with."[26]

- Pfizer CEO Dr. Bourla continued this warning in November 2021: "The only thing that stands between the new way of life and the current way of life, frankly, is the hesitancy to get vaccinated, the people that are afraid to get the vaccines, and they

[24] Celebrex Consent Judgment, ¶ 36; Lyrica Consent Judgment, ¶ 6.2; Rapamune Consent Judgment, ¶ 6.2; K.S.A. 50-631.

[25] *CNBC Transcript: Pfizer Chairman and CEO Albert Bourla Speaks with CNBC's 'Squawk Box' Today*, CNBC (Dec. 14, 2020), *at* https://www.cnbc.com/2020/12/14/cnbc-transcript-pfizer-chairman-and-ceo-albert-bourla-speaks-with-cnbcs-squawk-box-today.html.

[26] John Micklethwait, *Pfizer CEO Says Science Will Prevail with Covid-19 Here to Stay*, BLOOMBERG, Jan. 28, 2021, *at* https://www.bloomberg.com/news/features/2021-01-28/covid-is-here-to-stay-pfizer-ceo-albert-bourla.

> create issues not only for them. Unfortunately, they are going to affect the lives of others and, frankly, the lives of the people that they love the most because they are putting at risk the people that they hug, they kiss, [and] they socialize with."[27]

However, evaluating transmission was not an objective of Pfizer's COVID-19 trial protocol.[28]

Based on the contradictions between Pfizer's public statements and its trial protocol, it appears that Pfizer made false, misleading, or deceptive claims about its COVID-19 vaccine's effect on transmission in violation of the consent judgments with the State of Kansas.

Pursuant to the authority provided by consent judgments and Kansas law,[29] please provide, or make available for inspection and copying, the following documents within 30 days, by May 23, 2024:

1. All data Pfizer CEO Dr. Bourla relied on for his statements that not receiving Pfizer's COVID-19 vaccine would affect the lives of loved ones.

2. All emails between Pfizer personnel and the CDC, FDA, or White House from January 1, 2021 to October 1, 2021 relating to Pfizer's COVID-19 vaccine effect on transmission.

D. False, Misleading, or Deceptive Misinformation Claims

Pfizer appears to have coordinated directly and indirectly with social media platforms to remove information that was critical of Pfizer's COVID-19 vaccine.[30]

Pfizer's efforts to suppress and conceal material facts relating to its COVID-19 vaccine raise concerns that Pfizer made false, misleading, or deceptive claims about its COVID-19 vaccine in violation of the consent judgments with the State of Kansas. Pursuant to the authority provided by consent judgments and Kansas law,[31] please provide, or make available for inspection and copying, the following documents within 30 days, by May 23, 2024:

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[27] *Pfizer's Albert Bourla on how the pandemic ends*, ATLANTIC COUNCIL, Nov. 9, 2021, *at* https://www.atlanticcouncil.org/blogs/new-atlanticist/pfizers-albert-bourla-on-how-the-pandemic-ends/.

[28] Final C4591001 Protocol, "A Phase 1/2, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Adults," Pfizer, Apr. 15, 2020, 1 (PDF p. 3), *at* https://www.nejm.org/doi/suppl/10.1056/NEJMoa2027906/suppl_file/nejmoa2027906_protocol.pdf; Protocol C4591001, "A Phase 1/2/3, Placebo-Controlled, Randomized, Observer-Blind, Dose-Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals," Pfizer, Sept. 8, 2020 ("Sept. 2020 Protocol"), 1 (PDF p. 129), *at* https://www.nejm.org/doi/suppl/10.1056/NEJMoa2027906/suppl_file/nejmoa2027906_protocol.pdf.

[29] Celebrex Consent Judgment, ¶ 36; Lyrica Consent Judgment, ¶ 6.2; Rapamune Consent Judgment, ¶ 6.2; K.S.A. 50-631.

[30] *See, e.g.*, Alex Berenson, *From the Twitter Files: Pfizer board member Scott Gottlieb secretly pressed Twitter to hide posts challenging his company's massively profitable Covid jabs*, SUBSTACK, Jan. 9, 2023, *at* https://alexberenson.substack.com/p/from-the-twitter-files-pfizer-board.

[31] Celebrex Consent Judgment, ¶ 36; Lyrica Consent Judgment, ¶ 6.2; Rapamune Consent Judgment, ¶ 6.2; K.S.A. 50-631.

1. All documents and information provided by Pfizer to the United States House of Representatives Committee on the Judiciary in response to its July 18, 2023 request and any subsequent requests.[32]

2. All emails between Pfizer personnel and The Virality Project, including but not limited to Stanford Internet Observatory, the University of Washington's Center for an Informed Public, the Atlantic Council's Digital Forensic Research Lab, Graphika, the National Conference on Citizenship's Algorithmic Transparency Institute, and New York University's Center for Social Media and Politics and Tandon School of Engineering.

3. All emails between Pfizer and the Biotechnology Innovation Organization or the Public Good Project relating to the Public Good Project's "Stronger" campaign.

II. Inadequate study claims

As agreed in its consent judgment with Kansas, Pfizer's public communications about clinical study information must:

> (a) accurately reflect the methodology used to conduct the Clinical Study; (b) not present favorable information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions; and (c) not use statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluation.

Celebrex Consent Judgment, ¶ 10.

In addition, Pfizer's public communications about clinical study information must not:

> (a) present information from a study in a way that implies that the study represents larger or more general experience with the drug than it actually does; or (b) use statistics on numbers of patients, or counts of favorable results or side effects derived from pooling data from various insignificant or dissimilar studies in a way that suggests either that such statistics are valid if they are not or that they are derived from large or significant studies supporting favorable conclusions when such is not the case.

Id. at ¶ 11.

[32] Letter from U.S. House Judiciary Chairman Jim Jordan to Pfizer's Dr. Albert Bourla, July 18, 2023, *at* https://judiciary.house.gov/sites/evo-subsites/republicans-judiciary.house.gov/files/evo-media-document/2023-07-18-jdj-to-bourla-pfizer.pdf.

Pfizer appears to have made, or caused to be made, numerous claims about its COVID-19 vaccine's safety and effectiveness that are false, misleading, or deceptive and that violate these consent judgment provisions. The examples provided below are illustrative and are not intended to be an exhaustive list of all efficacy statements.

1. Pfizer excluded from its COVID-19 vaccine trials any individual with a medical or psychiatric condition that "may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study;"[33] any individual with a history of severe adverse reaction to vaccines;[34] any individual who had been diagnosed with COVID-19;[35] any immunocompromised individual;[36] and any woman who was pregnant or breastfeeding.[37]

2. When Pfizer sought approval for a third shot for its COVID-19 vaccine, it requested approval to vaccinate individuals 16 years of age and older, including the elderly. However, Pfizer only tested the booster shot on 12 trial participants who were in the 65- to 85-year-old age range.[38] Pfizer did not test the booster on any participant older than 85 years old.

Pfizer's representations that its COVID-19 vaccine was safe and effective for the general public violated its disclosure obligations under the consent judgment.

* * *

The State of Kansas looks forward to Pfizer providing the documents requested within 30 days and a good-faith written response to the issues raised in this letter within 30 days. The State of Kansas reserves its rights to take any necessary enforcement action.

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[33] Sept. 2020 Protocol, at 37 (PDF p. 165), ¶ 5.2.1.
[34] *Id.* at 37 (PDF p. 165), ¶ 5.2.3.
[35] *Id.* at 37 (PDF p. 165), ¶ 5.2.5.
[36] *Id.* at 38 (PDF p. 166), ¶ 5.2.8.
[37] *Id.* at 38 (PDF p. 166), ¶ 5.2.11.
[38] Vaccines and Related Biological Products Advisory Committee Meeting, Sept. 17, 2021, FDA Briefing Document, Application for licensure of a booster dose for COMIRNATY (COVID-19 Vaccine, mRNA), 22, *at* https://www.fda.gov/media/152176/download.

Sincerely,

Frances R. Oleen

Frances R. Oleen
Deputy Attorney General
Public Protection Division

Kaley Schrader

Kaley Schrader
Assistant Attorney General
Consumer Protection Section

Exhibit C

DLA Piper LLP (US)
500 Eighth Street, NW
Washington, DC 20004
www.dlapiper.com

Carl Wessel
Carlton.Wessel@us.dlapiper.com
T 202.799.4720
F 202.799.5706

May 22, 2024
VIA E-MAIL

CONFIDENTIAL TREATMENT REQUESTED BY PFIZER INC
EXEMPT UNDER THE KANSAS OPEN RECORDS ACT

Frances R. Oleen
Kaley Schrader
State of Kansas Office of the Attorney General
120 SW 10th Avenue, 2nd Floor
Topeka, Kansas 66612-1597

Re: Notice of Consent Judgment Violations

Dear Mss. Oleen and Schrader:

On behalf of our client, Pfizer Inc. ("Pfizer" or "the Company"), we write in response to your April 22, 2024 letter notifying Pfizer about alleged consent judgment violations. Pfizer hereby provides this good faith written response as requested in your letter.

Your letter alleges that Pfizer has made false, misleading, or deceptive claims regarding the Company's COVID-19 vaccine, as well as worked with social media platforms to suppress and conceal material facts about the vaccine, in violation of historical consent judgments relating to Celebrex (2008), Lyrica (2012), and Rapamune (2014). The Company disputes that these consent judgments apply to the COVID-19 vaccine and denies your allegations in the strongest possible terms.

The Company's public statements were consistent with and, in some cases, identical to the consensus view of global public health authorities. Among these are the U.S. Food & Drug Administration ("FDA"), which continues to endorse the safety and efficacy of the COVID-19 vaccine based on the totality of the scientific evidence, and the U.S. Centers for Disease Control and Prevention ("CDC"), which continues to recommend COVID-19 vaccinations for individuals aged 6 months and older to this very day. Your letter suggests the Kansas Attorney General's Office disagrees with FDA and CDC on these critical public health matters. Your Office may take a different view about the vaccine than federal regulatory authorities, but such disagreement does not create a violation of the consent judgments, nor does it render Pfizer's past statements about the vaccine false, misleading, or deceptive.

In our view, your letter draws incorrect conclusions about Pfizer's public statements as well as the overall safety and efficacy of the COVID-19 vaccine, and it takes words and phrases from Pfizer's voluminous public statements about the COVID-19 vaccine out of context. Pfizer stands behind its public statements concerning the safety and efficacy of the vaccine—including the specific statements identified in your letter—which were truthful, accurate, and non-misleading.

FACTUAL BACKGROUND

CDC issued its first publication identifying SARS-CoV-2, the novel coronavirus that causes the infectious disease now known as COVID-19, on January 10, 2020. Due to the rapid spread of this deadly, previously unknown virus, the World Health Organization declared COVID-19 a pandemic on March 11, 2020. Two days later, President Donald Trump declared COVID-19 a national emergency in the United States.

In the early months of the pandemic, there was no vaccine to protect against COVID-19. To address this urgent and unmet need, the Trump Administration launched Operation Warp Speed on May 15, 2020. Because large numbers of people were getting sick and dying from COVID-19, the federal government "refused to accept business-as-usual timelines for vaccines and other essential tools" and pledged, in collaboration with private industry, to "squeeze every last inefficiency out of the process and pour every resource" into an unprecedented effort to produce, among other things, hundreds of millions of doses of COVID-19 vaccines by January 2021.[1] This was an audacious, but necessary, goal; at the time, potential vaccine candidates, including Pfizer's, were still in the early phases of clinical development, and their prospects were uncertain.

In connection with Operation Warp Speed, FDA issued guidance to industry in June 2020 concerning the agency's expectations before it would consider licensing any COVID-19 vaccine candidate, including for Emergency Use Authorization ("EUA").[2, 3] "FDA would expect that a COVID-19 vaccine would prevent disease or decrease its severity in at least 50% of people who are vaccinated" before the agency would issue an EUA.

On July 27, 2020, Pfizer and its partner, BioNTech, launched the pivotal study that led to the current established efficacy and safety of the vaccine. This was a placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, immunogenicity, and efficacy of the Pfizer-BioNTech vaccine against COVID-19 in healthy individuals.[4] Approximately 40,000 participants were enrolled in the study at 153 clinical research sites. Under Pfizer's clinical trial protocol, about half of the participants received two

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[1] U.S. Dept. of Defense, Immediate Release: Trump Administration Announces Framework and Leadership for 'Operation Warp Speed,' May 15, 2020, https://tinyurl.com/3yajcvnd.

[2] U.S. Dept. of Health & Human Servs., Food & Drug Admin., Coronavirus (COVID-19) Update: FDA Takes Action to Help Facilitate Timely Development of Safe, Effective COVID-19 Vaccines, June 30, 2020, https://tinyurl.com/znavfbfp.

[3] U.S. Dept. of Health & Human Servs., Food & Drug Admin., Emergency Use Authorization for Vaccines to Prevent COVID-19 Guidance for Industry, Mar. 31, 2022, https://tinyurl.com/mrxhdwhu (referencing guidance from June 2020).

[4] A "placebo-controlled" trial is one in which there are at least two groups—one gets the active vaccine, the other gets the placebo, and everything else is held the same between the groups, so that any difference in their outcome can be attributed to the active vaccine. A "randomized" trial is one in which the participants are divided by chance into separate groups that compare different vaccines or other interventions. An "observer-blind" study is one in which those charged with measuring, recording, and assessing changes in research participants do not know which of the participants have received the active vaccine and which have received the placebo.

doses of the vaccine, with 21 days between each dose, and the remaining participants received placebo injections on the same schedule.

Pfizer and BioNTech announced initial results from the pivotal study, which showed a two-dose regimen of the vaccine demonstrated an efficacy rate above 90 percent from seven days after the second dose, in November 2020. Based on the results of the study, Pfizer and BioNTech asked FDA to authorize the vaccine for emergency use in individuals 16 years of age and older, and FDA issued the EUA on December 11, 2020.[5] President Trump called this authorization "really good news" and issued the following statement: "Today, our nation achieved a medical miracle. We have delivered a safe and effective vaccine in just nine months. It is one of the greatest scientific accomplishments in history. It will save millions of lives and soon end the pandemic once and for all."[6]

Immediately after receiving the EUA, Pfizer started shipping the first batches of the vaccine to the U.S. government, which had previously contracted to purchase 100 million doses of the vaccine upon FDA authorization or approval.[7] The government opted to provide the vaccine to the public for free, and the first doses of the vaccine were administered in the U.S. outside of the clinical trial setting on December 14, 2020.[8]

FDA has since issued additional EUAs for use of the Pfizer-BioNTech COVID-19 Vaccine in different age groups and for booster doses, and FDA approved the vaccine, now known by the brand name "Comirnaty," for individuals ages 16 and older on August 23, 2021.[9] The agency has since expanded Comirnaty's approval for adolescents 12 to 15 years of age.[10]

FDA has consistently expressed confidence in the safety and efficacy of the Pfizer-BioNTech vaccine in the face of politically motivated attacks. For example, FDA issued multiple letters to the Florida Department

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[5] U.S. Food & Drug Admin., FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine, Dec. 11, 2020, http://tinyurl.com/uz84ppkh.

[6] Anne Flaherty, et al., *FDA Authorizes 1st COVID-19 Vaccine in United States*, GOODMORNINGAMERICA.COM, Dec. 11, 2020, https://tinyurl.com/mr2hz895.

[7] Ben Guarino et al., *'The Weapon That Will End The War': First Coronavirus Vaccine Shots Given Outside Trials In U.S.*, WASH. POST, Dec. 14, 2020, https://tinyurl.com/4na9kyby.

[8] Ctrs. for Medicare & Medicaid Servs., Trump Administration Acts to Ensure Coverage of Life-Saving COVID-19 Vaccines & Therapeutics, Nov. 13, 2020, http://tinyurl.com/3w9btrdr.

[9] U.S. Food & Drug Admin., FDA Approves First COVID-19 Vaccine, Aug. 23, 2021, http://tinyurl.com/3wefvyy4; U.S. Food & Drug Admin., FDA Authorizes Booster Dose of Pfizer-BioNTech COVID-19 Vaccine for Certain Populations, Sept. 22, 2021, http://tinyurl.com/ky76zvm5; U.S. Food & Drug Admin., FDA Authorizes Bivalent Pfizer-BioNTech COVID-19 Vaccine as Booster Dose for Certain Children 6 Months through 4 Years of Age, Mar. 14, 2023, http://tinyurl.com/2p9uyj64.

[10] Pfizer Press Release, Pfizer and BioNTech Announce U.S. FDA Approval of their COVID-19 Vaccine Comirnaty For Adolescents 12 through 15 Years of Age, July 8, 2022, https://tinyurl.com/2vajxc9p.

of Health, most recently stating: "We stand firmly behind our regulatory decision making with the authorizations and approvals of the COVID-19 vaccines, which have a highly favorable safety profile, and which have saved, and continue to save, many lives."[11] In the same letter, FDA cautioned that "the challenge we continue to face is the ongoing proliferation of misinformation and disinformation about these vaccines which results in vaccine hesitancy," "lowers vaccine uptake," and "contribut[es] to the continued death and serious illness toll of COVID-19."

The Justice Department recently summarized the federal government's current position on the Pfizer and BioNTech COVID-19 vaccine, and vaccination in general, as follows:

> FDA has had continued access—as the information has become available—to the Pfizer COVID-19 vaccine clinical trial protocol and results, reported adverse event data and scientific research[.] . . . As recently as January 5, 2024, FDA Commissioner Robert Califf, MD and Director of FDA's Center for Biologics Evaluation and Research, Peter Marks, MD, Ph.D., published an editorial in the Journal of the American Medical Association reiterating the importance of vaccination, including vaccination to protect against COVID-19. They noted "contrary to a wealth of misinformation available on social media and the internet, data from various studies indicate that since the beginning of the COVID-19 pandemic tens of millions of lives [worldwide] were saved by vaccination."[12]

On a similar note, in February of this year, Dr. Marks testified before Congress that "COVID-19 vaccines have been shown to be safe. COVID-19 vaccines have been shown to be effective. They are supported by the best available scientific data; they underwent FDA's rigorous regulatory authorization and approval processes; and their safety over time is closely monitored."[13]

RESPONSE TO ALLEGATIONS

Your April 22, 2024 letter alleges that Pfizer appears to have made numerous claims about the Company's COVID-19 vaccine that are false, misleading, or deceptive. The primary focus of your letter is certain Pfizer press releases and other public statements that include references to the vaccine's safety profile. In particular, your letter suggests that Pfizer and BioNTech's COVID-19 vaccine is not safe because of alleged

[11] U.S. Food & Drug Admin., FDA Letter to Florida Department of Health Regarding COVID-19 Vaccine Safety, Dec. 14, 2023, http://tinyurl.com/3upwfz6k.

[12] U.S. Motion to Intervene and to Dismiss Pursuant to 31 U.S.C. § 3730(c)(2)(A), *United States ex rel. Jackson v. Ventavia Rsch. Grp., LLC*, Case No. 1:21-cv-00008, Dkt. 137 at 7–8 (E.D. Tex.) (quoting Peter Marks & Robert, Califf, *Is Vaccination Approaching a Dangerous Tipping Point?*, JAMA, Jan. 5, 2024, https://tinyurl.com/55x693u7).

[13] Assessing America's Vaccine Safety Systems, Part 1: Hearing Before Committee On Oversight And Accountability (Testimony of Dr. Peter Marks), Feb. 15, 2024, https://tinyurl.com/muf9aahk.

adverse event reports concerning (1) cardiovascular events like strokes, (2) myocarditis and pericarditis, and (3) adverse pregnancy outcomes.

The statements identified in your letter, when read in context and in light of the totality of scientific evidence available at the time, were truthful and non-misleading. Moreover, the identified statements are consistent with the letter and spirit of FDA's authorizations and approval of Pfizer and BioNTech's COVID-19 vaccine, as well as CDC's recommendations to the American people concerning vaccination against COVID-19. As such, the challenged statements cannot be considered false, misleading, or deceptive.

Cardiovascular Events

To challenge the vaccine's safety, your letter points to historical information about case reports containing hundreds of thousands of adverse events allegedly experienced by individuals who received Pfizer and BioNTech's COVID-19 vaccine, including some reports of cardiovascular events like strokes in people aged 65 and over. This statement and others like it in your letter are highly misleading. FDA and CDCrecently explained why in a communication to the Florida Surgeon General:[14]

- "The [FDA] and the [CDC] continue to diligently monitor a variety of data sources to identify any potential risks of the vaccines and to ensure that information is available to the public. That said, focusing on adverse events in the absence of causal association and without the perspective of countervailing benefits is a great disservice to both individuals and public health. Like every other medical intervention, there are adverse effects from vaccination. Serious adverse events from COVID-19 vaccines are rare and are far outweighed by the benefits of these vaccines for every age group."

- "***The claim that the increase of [] reports of life-threatening conditions reported from Florida and elsewhere represents an increase of risk caused by the COVID-19 vaccines is incorrect, misleading and could be harmful to the American public***. The FDA-approved and FDA-authorized COVID-19 vaccines have met FDA's rigorous scientific and regulatory standards for safety and effectiveness and these vaccines continue to be recommended for use by CDC for all people six months of age and older. Both FDA and CDC have continued to collect outcome data from multiple sources that demonstrate the clear benefit of COVID-19 vaccines in preventing death, serious illness, and hospitalization from SARS-CoV-2 infection, along with indicating a modest benefit in the prevention of infection and transmission that wanes over time, even as new variants have emerged. Additional benefits include a reduced risk of known complications from

[14] U.S. Ctrs. for Disease Control and Prevention, FDA and CDC Response to the Florida Surgeon General, Mar. 10, 2023, https://tinyurl.com/5n8tck2f (emphasis added).

SARS-CoV-2 infection, including post-COVID conditions, COVID-19-associated stroke and heart disease, and COVID-19-induced venous thromboembolism."

- "***Reports of adverse events . . . following vaccination do not mean that a vaccine caused the event***. Since December 2020, almost 270 million people have received more than 670 million doses of COVID-19 vaccines in the U.S., with over 50 million people having received the updated bivalent vaccine. The [EUAs] for the COVID-19 Vaccines require sponsors and vaccine providers to report certain adverse events through VAERS,[15] so more reports should be expected. Recent concerns about increased reports of cardiovascular events provide an instructive example of the need to do further analysis when increased reporting of an event occurs. ***Despite increased reports of these events, when the concern was examined in detail by cardiovascular experts, the risk of stroke and heart attack was actually lower in people who had been vaccinated, not higher***."

- "Adverse events must be compared to background rates in the population. . . . Based on available information for the COVID-19 vaccines that are authorized or approved in the United States, the known and potential benefits of these vaccines clearly outweigh their known and potential risks. Additionally, not only is there no evidence of increased risk of death following mRNA vaccines, but available data have shown quite the opposite: that being up to date on vaccinations saves lives compared to individuals who did not get vaccinated. ***Multiple well conducted, peer-reviewed, published studies . . . demonstrate that the risk of death, serious illness and hospitalization is higher for unvaccinated individuals for every age group***."

- "Because we are not the only country in the world using COVID-19 vaccines, we also benefit from the experience of other countries. More than 13 billion doses of COVID-19 vaccines have been given around the world, including hundreds of millions of doses of mRNA vaccines and hundreds of millions of doses to children. Consistent with our data, these multiple international partners have robust monitoring for both safety and effectiveness. They find little evidence of widespread adverse events, also detect rare events as we do, and conclude that the benefits of the vaccines generally far outstrip their risks."

Myocarditis and Pericarditis

Two of the rare events detected among individuals who received Pfizer's vaccine are myocarditis and pericarditis, predominantly in male adolescents and young adults. Your letter's suggestion that Pfizer has downplayed or concealed these issues is false. The Company has been fully transparent regarding adverse event reports concerning individuals who have received Pfizer's vaccine and, when public health authorities

[15] U.S. Ctrs. for Disease Control and Prevention, Vaccine Adverse Event Reporting System (VAERS), Oct. 19, 2023, https://tinyurl.com/3wdb623h.

noted a likely association in June 2021, Pfizer immediately revised the patient and provider fact sheets for the Pfizer-BioNTech COVID-19 Vaccine regarding the suggested increased risks of myocarditis and pericarditis following vaccination.

These safety risks continue to be prominently disclosed, including in the vaccine's current FDA-approved labeling, which provides: "Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae."[16]

While there is an increased risk of myocarditis for individuals who receive Pfizer's vaccine, there are data showing the overall risk of myocarditis is substantially higher immediately after being infected with the virus that causes COVID-19 than it is in the weeks following vaccination.[17] In other words, the risk of myocarditis from being infected by COVID-19 is far greater than the risk of myocarditis from receiving the vaccine. And, despite the warnings about myocarditis and pericarditis, CDC continues to recommend COVID-19 vaccinations, including Pfizer's vaccine, for individuals aged 6 months and older.[18]

Pregnancy and Fertility

CDC's recommendation explicitly extends to people who are pregnant, breastfeeding, trying to get pregnant now, or who might become pregnant in the future. The agency's website, which was last updated on March 8, 2024, is unequivocal: "COVID-19 vaccination during pregnancy is safe and effective," and "COVID-19 vaccines are not associated with fertility problems in women or men."[19] The same website provides that people who are pregnant or who were recently pregnant are: (1) "[m]ore likely to get very sick from COVID-19 compared to those who are not pregnant;" (2) "[m]ore likely to need hospitalization, intensive care, or the use of a ventilator or special equipment to breathe if [they] do get sick from COVID-19;" and (3) "[a]t

[16] Comirnaty Prescribing Information, https://tinyurl.com/5xmf8kck (last revised Oct. 2023).

[17] Hannah Rosenblum, M.D., Pfizer-BioNTech COVID-19 Vaccine and Myocarditis in Individuals Aged 16-29 Years: Benefits-Risk Discussion, Aug. 30, 2021, https://tinyurl.com/3zhkvfs2 (presentation to CDC's Advisory Committee on Immunization Practices stating the "[r]isk of myocarditis in individuals post-SARS-CoV-2 infection was 6-34 times higher compared to those who received mRNA vaccine").

[18] U.S. Ctrs. for Disease Control and Prevention, Myocarditis and Pericarditis After mRNA COVID-19 Vaccination, https://tinyurl.com/3tywzane (last updated Nov. 3, 2023).

[19] U.S. Ctrs. for Disease Control and Prevention, COVID-19 Vaccines While Pregnant or Breastfeeding, https://tinyurl.com/56uyfkmt (last updated Mar. 8, 2024).

increased risk of complications that can affect [their] pregnancy and baby including preterm birth or stillbirth."

The FDA-approved labeling for Pfizer and BioNTech's COVID-19 vaccine also states that a "developmental toxicity study has been performed in female rats administered the equivalent of a single human dose of Comirnaty . . . on 4 occasions" and the study "revealed no evidence of harm to the fetus due to the vaccine."[20]

The CDC website includes citations to "studies including hundreds of thousands of people around the world" showing that "COVID-19 vaccination before and during pregnancy is safe, effective, and beneficial to both the pregnant person and the baby." Per CDC, the cited studies establish that it is "safe to receive an mRNA COVID-19 vaccine (Moderna or Pfizer-BioNTech), before and during pregnancy" and these vaccines in particular "show no increased risk for complications like miscarriage, preterm delivery, stillbirth, or birth defects."

CDC's recommendations align with those from professional medical organizations including the American College of Obstetricians and Gynecologists,[21] the Society for Maternal Fetal Medicine,[22] and the American Society for Reproductive Medicine.[23] This expert consensus, along with the totality of the scientific evidence developed since the pandemic's onset, stand in stark contrast to your Office's unsupported suggestion that the vaccine is associated with "adverse pregnancy outcomes."

DOCUMENT REQUESTS

Your letter not only alleges that Pfizer violated the historical consent judgments, but also requests fourteen exceptionally broad categories of documents pursuant to Paragraph 36 of the Celebrex consent judgment, Paragraph 6.2 of the Lyrica consent judgment, and Paragraph 6.2 of the Rapamune consent judgment. These document requests are premature under the plain text of the consent judgments.

The Celebrex consent judgment, for example, states that the Attorney General's right of "reasonable access" to Pfizer's "relevant, non-privileged, non-work product records and documents" only attaches "[u]pon giving Pfizer thirty (30) days to respond" to the State's "written notice" of potential consent judgment violations. *See* Celebrex consent judgment, ¶¶ 35 & 36. The other consent judgments are substantially

[20] *See supra* n.16.

[21] Am. College of Obstetricians and Gynecologists, COVID-19 Vaccination Considerations for Obstetric–Gynecologic Care, Sept. 25, 2023, https://tinyurl.com/mpvr4pd4.

[22] Soc'y for Maternal Fetal Med., COVID-19 Vaccination in Pregnancy, Sept. 14, 2023, https://tinyurl.com/bp6cxtsr.

[23] Am. Society for Reproductive Med., Patient Management and Clinical Recommendations During the Coronavirus (COVID-19) Pandemic, Apr. 20, 2022, https://tinyurl.com/3vv539jw.

identical on this score. *See* Lyrica consent judgment, ¶¶ 6.1 & 6.2; Rapamune consent judgment, ¶¶ 6.1 & 6.2.

As previously stated, we do not believe the consent judgments apply to issues concerning the vaccine, but even if the consent judgments did apply, your requests for Pfizer's confidential documents are premature. If, after reviewing this letter, you continue to believe that review of documents would be helpful to your review, we would be happy to meet and confer with your Office about appropriate next steps.

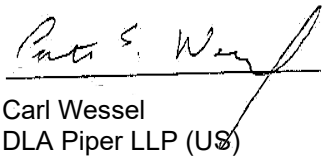
We look forward to discussing these issues with you further. Please do not hesitate to contact me.

* * *

Pfizer believes that this letter is protected from disclosure under the Kansas Open Records Act, K.S.A. 45-215, *et. seq*. Pfizer hereby requests that your Office, department, and all constituent agencies withhold any records or other material, including but not limited to this letter, containing or disclosing confidential commercial information, or law enforcement or investigative files, that relate to or reference Pfizer, under applicable exemptions or other provisions of the Kansas Open Records Act, and any other relevant statute or regulation. We further request that, if your Office believes disclosure is authorized by applicable law, it alert the recipient that the confidentiality of the information must be maintained.

We also hereby request that your Office, department, and all constituent agencies provide notice to us of any public records request for, or intended disclosure of, this letter. Pfizer also requests that your Office provide reasonably prompt notice to Pfizer, through its undersigned counsel, of any request by a third party for discovery of any part of this letter or of any proposal or apparent intention by a third party or your Office to enter any part of this letter in the public record, such notice to be provided reasonably in advance of satisfying any such discovery request or, to the extent possible, of any such entry in the public record, to enable Pfizer to seek confidential treatment of this letter or to seek relief in an appropriate court. Pfizer does not intend anything in this letter to affect any legal rights Pfizer may have to seek, in any proceeding in which your Office is a party, a protective order limiting dissemination of this letter by or to any third parties.

Very truly yours,



Carl Wessel
DLA Piper LLP (US)

Milton Marquis
Cozen O'Connor

Exhibit D

Meghan E. Stoppel, #23685
Assistant Attorney General
Office of the Kansas Attorney General
120 SW 10th Avenue, 2nd Floor
Topeka, Kansas 66612
(785) 296-3751

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KS. DISTRICT COURT
THIRD JUDICIAL DIST.
TOPEKA, KS

2012 DEC 13 P 4:03

IN THE DISTRICT COURT OF SHAWNEE COUNTY, KANSAS
Division 6

STATE OF KANSAS, *ex rel.*	)	
DEREK SCHMIDT, Attorney General,	)	
	)	
Plaintiff,	)	
	)	
v.	)	**Case No.** 12C1339
	)	
PFIZER INC,	)	
	)	
Defendant.	)	
	)	

(Pursuant to K.S.A. Chapter 60)

JOURNAL ENTRY OF CONSENT JUDGMENT

NOW on this 13th day of December, 2012, Plaintiff's Journal Entry of Consent Judgment comes before the Court pursuant to K.S.A. 50-632(b). The Plaintiff, State of Kansas, *ex rel.* Derek Schmidt, Attorney General, appears by and through Meghan E. Stoppel, Assistant Attorney General. Defendant Pfizer Inc (hereinafter "Pfizer") appears by and through the undersigned counsel.

WHEREUPON the parties advise the Court that they have stipulated and agreed to the following:

PARTIES, JURISDICTION AND VENUE

1. Derek Schmidt is the duly elected, qualified and acting Attorney General for the State of Kansas.

2. The Attorney General's authority to bring this action is derived from the statutory and common law of the State of Kansas, specifically the Kansas Consumer Protection Act, K.S.A. 50-623 *et seq.*

3. At all times relevant hereto, Pfizer engaged in "consumer transactions" in Kansas, as defined by K.S.A. 50-624(c).

4. Venue is proper under K.S.A. 50-638 in the Third Judicial District of Kansas (Shawnee County).

IT IS HEREBY ORDERED THAT:

1. FINDINGS

1.1 This Court has jurisdiction over the subject matter of this lawsuit and over all Parties, pursuant to the Kansas Consumer Protection Act, K.S.A. 50-623 *et seq.*

1.2 The terms of this Judgment shall be governed by the laws of the State of Kansas.

1.3 Entry of this Judgment is in the public interest and reflects a negotiated agreement among the Parties.

1.4 The Parties have agreed to resolve the issues resulting from the Covered Conduct involving the prescription drugs Zyvox® and Lyrica® by entering into this Judgment.

1.5 Pfizer is willing to enter into this Judgment regarding the Covered Conduct in order to resolve the Attorneys General's concerns under the State Consumer Protection Laws as to the matters addressed in this Judgment and thereby avoid significant expense, inconvenience, and uncertainty.

1.6 The Parties have agreed to resolve the issues raised by the Covered Conduct by entering into this Judgment.[1]

A. Pfizer is entering into this Judgment solely for the purpose of settlement, and nothing contained herein may be taken as or construed to be an admission or concession of any violation of law, rule, or regulation, or of any other matter of fact or law, or of any liability or wrongdoing, all of which Pfizer expressly denies. Pfizer does not admit any violation of the State Consumer Protection Laws set forth in footnote 3, and does not admit any wrongdoing that was or could have been alleged by any Attorney General before the date of the Judgment under those laws. No part of this Judgment, including its statements and commitments, shall constitute evidence of any liability, fault, or wrongdoing by Pfizer. This document and its contents are not intended for use by any third party for any purpose, including submission to any court for any purpose.

B. This Judgment shall not be construed or used as a waiver or limitation of any defense otherwise available to Pfizer in any action, or of Pfizer's right to defend itself from, or make any arguments in, any private individual, regulatory, governmental, or class claims or suits relating to the subject matter or terms of this Judgment. This Judgment is made without trial or adjudication of any issue of fact or law or finding of liability of any kind. Notwithstanding the foregoing, a State may file an action to enforce the terms of this Judgment.

C. It is the intent of the Parties that this Judgment not be admissible in other cases or binding on Pfizer in any respect other than in connection with the enforcement of this Judgment.

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[1] This agreement is entered into pursuant to and subject to the State Consumer Protection laws cited in footnote 3.

D. No part of this Judgment shall create a private cause of action or confer any right to any third party for violation of any federal or state statute except that a State may file an action to enforce the terms of this Judgment.

1.7 This Judgment (or any portion thereof) shall in no way be construed to prohibit Pfizer from making representations with respect to any Pfizer Product that are required under Federal law or Regulations or in Food and Drug Administration ("FDA") approved Labeling.

1.8 Nothing in this Judgment shall require Pfizer to:

(a) take any action that is prohibited by the Food, Drug and Cosmetic Act, 21 U.S.C. §301 *et seq*. ("FDCA") or any regulation promulgated thereunder, or by the FDA; or

(b) fail to take any action that is required by the FDCA or any regulation promulgated thereunder, or by the FDA. Any written or oral Promotional claim subject to this Judgment/Order which is the same, or materially the same, as the language required or agreed to by the Director of the Office of Prescription Drug Promotion, the Director of the Advertising and Promotional Labeling Branch, the Director of the Center for Drug Evaluation and Research, or the Director of the Center for Biologics Evaluation and Research, or their authorized designees in writing shall not constitute a violation of this Judgment, unless facts are or become known to Pfizer that cause the claim to be false, misleading, or deceptive.

2. DEFINITIONS

The following definitions shall be used in construing this Judgment:

2.1 "Clearly and Conspicuously" shall mean a disclosure in size, color, contrast, font, and location that is readily noticeable, readable and understandable and is presented in proximity to all information necessary to prevent it from being misleading or deceptive. A statement may

not contradict or be inconsistent with any other information with which it is presented. If a statement modifies, explains, or clarifies other information or is necessary to prevent other information from being misleading or deceptive, then the statement must be presented in close proximity to that information, in a manner that is readily noticeable, readable, and understandable, and it must not be obscured in any manner.

2.2 "Covered Conduct" shall mean Pfizer's Promotional and marketing practices, sampling practices, and dissemination of information and remuneration to HCPs regarding the prescription drugs Zyvox® and Lyrica® through the Effective Date of the Judgment.

2.3 "Effective Date" shall mean the date on which a copy of this Judgment, duly executed by Pfizer and by the Signatory Attorney General, is approved by, and becomes a Judgment of the Court.

2.4 "FDA Guidances for Industry" shall mean final documents issued by the FDA pursuant to 21 U.S.C. §371(h) that represent the FDA's current thinking on a topic.

2.5 "Health Care Professional" or "HCP" shall mean any physician or other health care practitioner, who is licensed to provide health care services or to prescribe pharmaceutical products.

2.6 "Healthcare Organization" shall mean an entity, public or private, that is intended and incentivized to tie patient care to quality metrics and value models and includes organizations such as payors, Health Maintenance Organizations (HM), Long Term Care (LTC) pharmacy providers, Pharmacy Benefit Management (PBM), Integrated Delivery Networks (IDN), Accountable Care Organizations (ACO), and hospital formulary committees.

2.7 "Labeling" shall mean all FDA-approved labels and other written, printed, or graphic matter (a) upon any article or any of its containers or wrappers, or (b) accompanying such article.

2.8 "Lyrica®" shall mean all Pfizer Products that are FDA-approved drug formulations containing pregabalin.

2.9 "Medical Information Response" shall mean a non-Promotional, scientific communication to address Unsolicited Requests for medical information from HCPs.

2.10 "Medical Outcome Specialists" shall mean Pfizer personnel who work with Healthcare Organizations that determine the drugs to be placed on a formulary.

2.11 "Multistate Executive Committee" shall mean the Attorneys General and their staffs representing Arizona, Illinois, Maryland, New Jersey, Pennsylvania, South Carolina, and Texas.

2.12 "Multistate Working Group" shall mean the Attorneys General and their staff representing Alabama, Arizona, Arkansas, California, Colorado, Delaware, District of Columbia, Florida, Hawaii, Idaho, Illinois, Indiana, Kansas, Kentucky, Maryland, Michigan, Montana, Nebraska, Nevada, New Jersey, New Mexico, North Carolina, Ohio, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Vermont, Virginia, Washington, and Wisconsin.[2]

[2] Hawaii is being represented on this matter by its Office of Consumer Protection, an agency which is not part of the state Attorney General's Office, but which is statutorily authorized to undertake consumer protection functions, including legal representation of the State of Hawaii. For simplicity, the entire group will be referred to as the "Attorneys General," and such designation, as it includes Hawaii, refers to the Executive Director of the State of Hawaii Office of Consumer Protection.

2.13 "Off-Label" shall mean a use related to an indication that was not approved by the FDA or information that was not contained in the FDA label at the time information regarding such use was communicated.

2.14 "Parties" shall mean Pfizer and the Signatory Attorney General.

2.15 "Pfizer Inc" or "Pfizer" shall mean Pfizer Inc, including all of its affiliates over which it has a controlling interest, subsidiaries and divisions, predecessors, successors, and assigns doing business in the United States.

2.16 "Pfizer Marketing" shall mean Pfizer personnel responsible for marketing Zyvox® or Lyrica® in the United States.

2.17 "Pfizer Medical" shall mean Pfizer personnel assigned to the Pfizer medical organization, including those personnel assigned to Pfizer's Medication Information Department ("USMI") or any successor group performing the same functions as the USMI.

2.18 "Pfizer Product" or "Product" shall mean any FDA-approved prescription drug or biological product manufactured, distributed, sold, marketed or Promoted by Pfizer in the United States.

2.19 "Pfizer Sales" shall mean the Pfizer sales force responsible for U.S. Zyvox® or Lyrica® sales, including, but not limited to, the field force and all management personnel such as district managers, regional managers, vice president(s) over sales, and president over sales.

2.20 "Promotional," "Promoting," or "Promote" shall mean representations about a Pfizer Product and other practices intended to increase sales or that attempt to influence prescribing practices of HCPs, including direct-to-consumer.

2.21 "Promotional Materials" shall mean any item used to Promote Zyvox® or Lyrica®

2.22 "Promotional Media" shall mean Promotional Materials in any media format for use in speaker programs.

2.23 "Promotional Speaker" shall mean an HCP speaker engaged by Pfizer to Promote Zyvox® or Lyrica® .

2.24 "Reprints Containing Off-Label Information" shall mean articles or reprints from a scientific or medical journal, as defined in 21 C.F.R. 99.3(j), or reference publication, as defined in 21 C.F.R. 99.3(i), describing an Off-Label use of Zyvox® or Lyrica®.

2.25 "Signatory Attorney General" shall mean the Attorney General of Kansas, or his/her authorized designee, who has agreed to this Judgment.

2.26 "State Consumer Protection Laws" shall mean the consumer protection laws cited in footnote 3 under which the Attorneys General have conducted the investigation.[3]

---

[3] ALABAMA – *Alabama Deceptive Trade Practices Act* § 8-19-1 *et. seq.* (2002); ARIZONA – *Arizona Consumer Fraud Act*, A.R.S. § 44-1521 *et seq.*; ARKANSAS – Arkansas Deceptive Trade Practices Act, Ark. Code Ann. § 4-88-101, *et seq.*; CALIFORNIA – Bus. & Prof Code §§ 17200 *et seq.* and 17500 *et seq.*; COLORADO – *Colorado Consumer Protection Act*, Colo. Rev. Stat. § 6-1-101 *et seq.*; DELAWARE – *Delaware Consumer Fraud Act*, Del. CODE ANN. tit. 6, §§ 2511 to 2536; DISTRICT OF COLUMBIA, *District of Columbia Consumer Protection Procedures Act*, D.C. Code §§ 28-3901 *et seq.*; FLORIDA – *Florida Deceptive and Unfair Trade Practices Act, Part II*, Chapter 501, Florida Statutes, 501.201 *et. seq.*; HAWAII – *Uniform Deceptive Trade Practice Act*, Haw. Rev. Stat. Chpt. 481A and Haw. Rev. Stat.Chpt. 480 [501.201 *et seq.*]; IDAHO – *Consumer Protection Act*, Idaho Code Section 48-601 *et seq.*; ILLINOIS – *Consumer Fraud and Deceptive Business Practices Act*, 815 ILCS 505/2 *et seq.*; INDIANA – *Deceptive Consumer Sales Act*, I.C. §24-5-0.5 *et seq.*; KANSAS - *Kansas Consumer Protection Act*, K.S.A. 50-623 et seq. KENTUCKY – *Kentucky Consumer Protection Act*, KRS Ch. 367.110, *et seq.*; MARYLAND - *Maryland Consumer Protection Act*, Md. Code Ann., Com. Law §§ 13-101 *et seq.*; MICHIGAN – *Michigan Consumer Protection Act*, MCL § 445.901 *et seq.*; MONTANA – Montana Code Annotated 30-14-101 *et seq.*; NEBRASKA – *Uniform Deceptive Trade Practices Act*, NRS §§ 87-301 *et seq.*; NEVADA – Deceptive Trade Practices Act, Nevada Revised Statutes 598.0903 *et seq.*; NEW JERSEY – *New Jersey Consumer Fraud Act*, NJSA 56:8-1 *et seq.*; NEW MEXICO – NMSA 1978, § 57-12-1 *et seq.*; NORTH CAROLINA – North Carolina Unfair and Deceptive Trade Practices Act, N.C.G.S. 75-1.1, *et seq.*; OHIO – *Ohio Consumer Sales Practices Act*, R.C. 1345.01, *et seq.*; PENNSYLVANIA – *Pennsylvania Unfair Trade Practices and Consumer Protection Law*, 73 P.S. 201-1 *et seq.*; RHODE ISLAND – *Rhode Island Deceptive Trade Practices Act*, Rhode Island General laws § 6-13.1-1 *et seq.* ; SOUTH CAROLINA – *South Carolina Unfair Trade Practices Act*, sections 39-5-10 *et seq.*; SOUTH DAKOTA – *South Dakota Deceptive Trade Practices and Consumer Protection*, SDCL ch. 37-24; TENNESSEE – *Tennessee Consumer Protection Act*, Tenn. Code Ann. 47-18-101 *et seq.*; TEXAS – *Texas Deceptive Trade Practices-Consumer Protection Act*, Tex. Bus. And Com. Code 17.41, *et seq.*; VERMONT – *Consumer Fraud Act*, 9 V.S.A. §§ 2451 *et seq.*; VIRGINIA-*Virginia Consumer Protection Act*, Va Code Ann. §59.1-196 *et seq.*; WASHINGTON – *Unfair Business Practices/Consumer Protection Act*, RCW §§ 19.86 *et seq.*; WEST VIRGINIA – *West Virginia Consumer Credit and Protection Act*, W. Va. Code § 46A-1101 *et seq.;* WISCONSIN – Wis. Stat. § 100.18 (Fraudulent Representations).

2.27 "Unsolicited Request" shall mean a request for information regarding Zyvox® or Lyrica® communicated to an agent of Pfizer that has not been prompted by or on behalf of Pfizer.

2.28 "Zyvox®" shall mean all Pfizer Products that are FDA-approved drug formulations containing linezolid.

2.29 Any reference to a written document shall mean a physical paper copy of the document, an electronic version of the document, or electronic access to such document.

3. COMPLIANCE PROVISIONS

IT IS FURTHER ORDERED, ADJUDGED AND DECREED THAT:

Promotional Activities

3.1 Pfizer shall not make, or cause to be made, any written or oral claim that is false, misleading, or deceptive regarding any FDA-approved Pfizer Product, including, but not limited to, any false, misleading, or deceptive claim when comparing the efficacy or safety of Zyvox® to vancomycin.

3.2 Pfizer shall not make any claim comparing the safety or efficacy of a Pfizer Product to another product when that claim is not supported by substantial evidence as defined by Federal law and regulations.

3.3 Pfizer shall not Promote Zyvox® or Lyrica® to an HCP who practices in a specialty that is unlikely to prescribe for a use in Zyvox®'s or Lyrica®'s FDA approved Labeling.

3.4 Pfizer shall not make any written or oral Promotional claim of safety or effectiveness for any Pfizer Product in a manner that violates the FDCA, accompanying

regulations, or voluntary agreements with FDA, as interpreted by the FDA in a writing by the Director of the Center for Drug Evaluation at the FDA.

3.5 Pfizer shall not Promote any Pfizer Product for Off-Label uses.

3.6 Pfizer shall not present patient profiles/types based on selected symptoms of the FDA-approved indication(s) when Promoting Zyvox® or Lyrica® for six years from the Effective Date of this Judgment, unless:

A. Zyvox®'s or Lyrica®'s specific FDA-approved indication(s) is/are stated Clearly and Conspicuously in the same spread (e.g. on the same page or on a facing page) in any Promotional Materials that reference the selected symptoms;

B. Promotional Materials have a statement indicating that prescribers should take into consideration the full range of a patient's symptoms and other relevant information before making a treatment decision.

3.7 Pfizer shall not make any claim that contradicts or minimizes a precaution, warning, or adverse reaction that is described in product Labeling for Zyvox® or Lyrica®.

3.8 In Promotional Materials, Pfizer shall Clearly and Conspicuously disclose all material facts regarding the following: the risks associated with Zyvox® or Lyrica® as set forth in the products' FDA- approved Labeling; information in any boxed warning; and facts about the negative consequences and side effects that can result from use of Zyvox® or Lyrica®. Pfizer shall present information about effectiveness and risk in a balanced manner. Whenever Pfizer knows or has reason to believe the current Labeling does not reflect the efficacy or risks of Zyvox® or Lyrica®, Pfizer shall promptly notify the Food and Drug Administration.

3.9 Pfizer shall not affirmatively seek the inclusion of Zyvox® or Lyrica® in hospital protocols or standing orders unless Zyvox® or Lyrica® has been approved by the FDA for the indication for which it is to be included in the protocol or standing order.

3.10 Pfizer shall require that all Promotional Speakers comply with Pfizer's obligations in paragraphs 3.1 through 3.8, 3.26, and 3.33 of this Judgment, including, but not limited to, ensuring that all Promotional Speakers' Promotional Materials and Promotional Media for Zyvox® and Lyrica® comply with Pfizer's obligations in this Judgment.

3.11 Pfizer shall notify its sales force promptly of any warning letter received from the FDA which affects the conduct of any sales representative in Promoting the relevant Pfizer Product and shall promptly provide a detailed explanation of the effect of the letter on the Promotion of Pfizer Products.

Financial incentives to Pfizer Sales, Medical Outcome Specialists, and/or Marketing

3.12 Pfizer's financial incentives shall be designed to ensure that Pfizer Sales, Medical Outcome Specialists, and/or Pfizer Marketing are not motivated to engage in improper Promoting, selling, and marketing of Zyvox® or Lyrica®.

3.13 Pfizer's financial incentives shall not include mechanisms to provide incentive compensation for sales that may be attributable to the Off-Label uses of any Pfizer Product.

3.14 For six years from the Effective Date of this Judgment, Pfizer shall continue to implement measures whereby sales goals for Zyvox® or Lyrica® can be met without including Off-Label prescriptions.

3.15 For six years from the Effective Date of this Judgment, Pfizer shall not award prizes or other incentives to its sales force as rewards for the Off-Label sale or use of any FDA-approved Pfizer Product.

Dissemination and Exchange of Medical Information

The following provisions shall be effective for six years from the Effective Date of this Judgment.

3.16 Pfizer shall not knowingly disseminate any Medical Information Response, including one that describes any Off-Label use of Zyvox® or Lyrica®, that makes any false, misleading, or deceptive representation regarding Zyvox® or Lyrica® or any false, misleading, or deceptive statement concerning a competing product.

3.17 Pfizer Sales, Pfizer Marketing, and Medical Outcomes Specialists shall not develop the medical content of Medical Information Responses regarding Zyvox® or Lyrica®. Notwithstanding the foregoing, Medical Outcomes Specialists may assist in the development of pharmacoeconomic content of Medical Information Responses.

3.18 Medical Information Responses to Unsolicited Requests for Off-Label information regarding Zyvox® or Lyrica® may be disseminated only by Pfizer Medical.

3.19 Pfizer Medical shall have ultimate responsibility for developing and approving all Medical Information Responses regarding Zyvox® or Lyrica®. Additional approvals may be provided by Pfizer's legal department. Pfizer shall not distribute any such materials unless:

A. Clinically relevant information is included in these materials to provide scientific balance;

B. Data in these materials are presented in an unbiased, non-Promotional manner; and

C. These materials are clearly distinguishable from sales aids and other Promotional Materials.

Responses to Unsolicited Requests for Off-Label Information

The following provisions shall be effective for six years from the Effective Date of this Judgment.

3.20 If Pfizer elects to respond to an Unsolicited Request for Off-Label information Pfizer Medical shall provide specific, accurate, objective, and scientifically balanced responses. Any such response shall not Promote Zyvox® or Lyrica® for any Off-Label use(s).

3.21 Any written Pfizer response to an Unsolicited Request for Off-Label information regarding Zyvox® or Lyrica® shall be a Medical Information Response and shall include:

A. A copy of the FDA-required Labeling, if any, for the product (e.g., FDA-approved package insert and, if the response is for a consumer, FDA-approved patient labeling);

B. A prominent statement notifying the recipient that the FDA has not approved or cleared the product as safe and effective for the Off-Label use addressed in the accompanying materials;

C. A prominent statement disclosing the indication(s) for which FDA has approved or cleared the product;

D. A prominent statement providing all important safety information including, if applicable, any boxed warning for the product;

E. Non-biased information or data relating to the particular Off-Label use that is the subject of the request, including applicable data that are not supportive or that cast doubt on the safety or efficacy of that use; and

F. A comprehensive list of references for all of the information disseminated in the response (e.g., a bibliography of publications in peer-reviewed medical journals or in medical or scientific texts; citations for data on file, for summary documents, or for abstracts).

3.22 Pfizer Sales, Pfizer Marketing, and Medical Outcome Specialists may respond orally to an Unsolicited Request for Off-Label information regarding Zyvox® or Lyrica® only by offering to request on behalf of the HCP that a Medical Information Response be sent to the HCP in follow up or by offering to put the HCP in touch with Pfizer Medical. Notwithstanding the foregoing, Medical Outcomes Specialists may respond to inquiries related to pharmacoeconomics or health outcomes from formulary decision makers or the groups responsible for the management of health benefits within Healthcare Organizations, but not prescribers unless employed or engaged by a Healthcare Organizationin a role connected to formulary decisions or the management of health benefits.

3.23 Information distributed by USMI in response to an Unsolicited Request for Off-Label information shall be:

A. Provided only to the individual making the request;

B. Tailored to answer only the specific Off-Label question(s) asked;

C. Scientific in nature; and

D. Unaccompanied by other material or information that is Promotional in nature or tone.

Reprints

3.24 Pfizer shall not disseminate any information describing any Off-Label use of any Pfizer Product if such use has been submitted to the FDA for approval and the FDA has either advised Pfizer that it refuses to approve such application or that FDA-identified deficiencies must be resolved before approval can be granted unless Pfizer has first Clearly and Conspicuously disclosed to the recipient of the information that the FDA has issued such advice. Pfizer may disclose to any recipient of such information whether the information was presented to the FDA prior to the FDA's issuance of such advice regarding the Off-Label use.

3.25 Pfizer shall not disseminate information describing any Off-Label or unapproved use of Zyvox® or Lyrica® unless such information and materials comply with applicable FDA regulations and the recommended actions in FDA Guidances for Industry.

3.26 Reprints Containing Off-Label Information

A. Pfizer Medical shall be responsible for the identification, selection, approval and dissemination of Reprints Containing Off-Label Information regarding Zyvox® or Lyrica®.

B. Reprints Containing Off-Label Information regarding Zyvox® or Lyrica®:

(i) shall be accompanied by the FDA approved Labeling for the product and contain a disclosure in a prominent location, which would

include the first page or as a cover page where practicable, indicating that the article may discuss Off-Label information; and

(ii) shall not be referred to or used in a Promotional manner.

C. Reprints Containing Off-Label Information regarding Zyvox® or Lyrica® may only be disseminated by Pfizer Medical to HCPs. Notwithstanding the foregoing, Medical Outcomes Specialists may disseminate reprints relating to pharmacoeconomics or health outcomes to formulary decision makers or the groups responsible for the management of health benefits within Healthcare Organizations, but not prescribers unless employed or engaged by a Healthcare Organization in a role connected to formulary decisions or the management of health benefits.

3.27 Nothing in this Judgment shall preclude Pfizer from disseminating reprints which have only an incidental reference to Off-Label information. If reprints have an incidental reference to Off-Label information, such reprints shall not be subject to the requirements of Section 3.24 and such incidental reference to Off-Label information shall not be referred to or used in a Promotional manner as prohibited by Section 3.26. B.ii.

Product Samples

The following provisions shall be effective for six years from the Effective Date of this Judgment.

3.28 Pfizer shall only provide samples of Zyvox® or Lyrica® to those HCPs who have specialties that customarily treat patients who have diseases for which treatment with Zyvox® or Lyrica® would be consistent with that product's FDA- approved Labeling.

3.29 Pfizer shall not disseminate samples of Zyvox® or Lyrica® with the intent of increasing Off-Label prescribing.

Sales Force Monitoring

3.30 Pfizer shall maintain a compliance program consistent with its Corporate Integrity Agreement signed on August 31, 2009 that includes a chief compliance officer; a compliance committee; a written code of conduct; written policies and procedures; education and training initiatives; a disclosure program that allows for confidential disclosure and investigation of potential compliance violations and appropriate disciplinary procedures; and regular internal auditing procedures. The compliance program shall include a sales force monitoring program designed to directly and indirectly observe the appropriateness of the sales force's interactions with HCPs and to identify potential Off-Label Promotional activities. The sales force monitoring program shall also include a Promotional speaker monitoring program, direct field observations of the sales force, and the monitoring and review of other records related to the sales force's interactions with HCPs. Pfizer's sales force monitoring program shall also include a centralized electronic system to be used by the sales force in connection with the detailing of HCPs that is consistent with the Corporate Integrity Agreement signed on August 31, 2009. The centralized electronic system shall include a detailing system that allows for and does not discourage the entry of free text summaries of interactions with HCPs. This paragraph shall be effective until December 31, 2014.

3.31 Pfizer shall maintain a disclosure program which allows for the anonymous disclosure of compliance policy violations and contains a nonretaliation policy.

Clinical Research

3.32 Pfizer shall report clinical research regarding Zyvox® and Lyrica® in an accurate, objective and balanced manner, and as required by applicable law. For all Pfizer-sponsored clinical trials and to the extent permitted by the National Library of Medicine, Pfizer shall register clinical trials and submit clinical trial results to the federal clinical trial registry and results data bank regarding Zyvox® and Lyrica® on the publicly accessible NIH website (www.clinicaltrials.gov) as required by the FDA Amendments Act of 2007, Public Law No. 110-85, 121 Stat 823, and any accompanying regulations that may be promulgated pursuant to that Act.

3.33 When presenting information about a clinical study regarding Zyvox® or Lyrica® in any Promotional materials, Pfizer shall not do any of the following:

A. Present information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions;

B. Use the concept of statistical significance to support a claim that has not been demonstrated to have clinical significance or validity or fails to reveal the range of variations around the cited average results;

C. Use statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from the study the design or protocol of which is not amenable to formal statistical evaluations;

D. Present the information in a way that implies that the study represents larger or more general experience with the drug than it actually does;

E. Use statistics on numbers of patients, or counts of results or side effects, derived from pooling data from various insignificant or dissimilar studies in a way that suggests either that such statistics are valid if they are not or that they are derived from large or significant studies supporting favorable conclusions when such is not the case. If any results derived from pooling data are presented, Pfizer shall disclose the method of pooling;

F. Use tables or graphs to distort or misrepresent the relationships, trends, differences, or changes among the variables or products studied; or

G. Use reports or statements represented to be statistical analyses, interpretations, or evaluations that are inconsistent with or violate the established principles of statistical theory, methodology, applied practice and inference, or that are derived from clinical studies the design, data, or conduct of which substantially invalidate the application of statistical analyses, interpretation, or evaluation.

4. PAYMENT

4.1 No later than 30 days after the Effective Date of this Judgment, Pfizer shall pay a total amount of Forty-Two Million Nine Hundred Thousand Dollars ($42,900,000.00) to be divided and paid by Pfizer directly to each Signatory Attorney General of the Multistate Working Group in an amount to be designated by and in the sole discretion of the Multistate Executive Committee. Said payment shall be used by the States as attorneys' fees and other costs of

investigation and litigation, or to be placed in, or applied to, the consumer protection enforcement fund, including future consumer protection enforcement, consumer education, litigation or local consumer aid fund or revolving fund, used to defray the costs of the inquiry leading hereto, at the sole discretion of each Signatory Attorney General. The Parties acknowledge that the payment described herein is not a fine, penalty, or payment in lieu thereof.

5. RELEASE

5.1 By its execution of this Judgment, the State of Kansas releases Pfizer and all of its past and present affiliates over which it has a controlling interest, subsidiaries and divisions, predecessors, successors, and assigns (collectively, the "Released Parties") from the following: all civil claims, causes of action, damages, restitution, fines, costs, and penalties that the Kansas Attorney General has asserted or could have asserted against the Released Parties under the Kansas Consumer Protection Act, K.S.A. 50-623 *et seq*. resulting from the Covered Conduct up to and including the Effective Date.

5.2 Notwithstanding any term of this Judgment, specifically reserved and excluded from the release in Paragraph 5.1 as to any entity or person, including Released Parties, are any and all of the following:

A. Any criminal liability that any person and/or entity, including Released Parties, has or may have to the State of Kansas.

B. Any civil or administrative liability that any person and/or entity, including Released Parties, has or may have to the State of Kansas not expressly covered by the release in Paragraph 5.1 above, including, but not limited to, any and all of the following claims:

i) State or federal antitrust violations;

ii) Claims involving "best price", "average wholesale price," "wholesale acquisition cost," or any reporting practices;

iii) Medicaid claims, including, but not limited to, federal Medicaid drug rebate statute violations, Medicaid fraud or abuse, and/or kickback violations related to any State's Medicaid program;

iv) State false claims violations; and

v) Actions on behalf of state program payors of the State of Kansas arising from the purchase of a Pfizer Product.

C. Any liability under the Kansas Consumer Protection Act, K.S.A. 50-623 *et seq*. which any person and/or entity, including Released Parties, has or may have to individual consumers.

5.3 Nothing contained in this Judgment shall relieve Pfizer of the obligations it maintains under any other Judgment or agreement relating to any Pfizer Product.

6. DISPUTE RESOLUTION

6.1 For the purposes of resolving disputes with respect to compliance with this Judgment, should any of the Signatory Attorneys General have a reasonable basis to believe that Pfizer has engaged in a practice that violates a provision of this Judgment subsequent to the Effective Date of this Judgment, then such Attorney General shall notify Pfizer in writing of the specific objection, identify with particularity the provision of this Judgment that the practice appears to violate, and give Pfizer thirty (30) days to respond to the notification; provided, however, that a Signatory Attorney General may take any action if the Signatory Attorney

General concludes that, because of the specific practice, a threat to the health or safety of the public requires immediate action. Upon receipt of written notice, Pfizer shall provide a good-faith written response to the Attorney General notification, containing either a statement explaining why Pfizer believes it is in compliance with the Judgment, or a detailed explanation of how the alleged violation occurred and a statement explaining how Pfizer intends to remedy the alleged breach. Nothing in this section shall be interpreted to limit the state's Civil Investigative Demand ("CID") or investigative subpoena authority, to the extent such authority exists under applicable law, and Pfizer reserves all of its rights in responding to a CID or investigative subpoena issued pursuant to such authority.

6.2 Upon giving Pfizer thirty (30) days to respond to the notification described above, the Signatory Attorney General shall also be permitted reasonable access to inspect and copy relevant, non-privileged, non-work product records and documents in the possession, custody, or control of Pfizer that relate to Pfizer's compliance with each provision of this Judgment pursuant to that State's CID or investigative subpoena authority. If the Signatory Attorney General makes or requests copies of any documents during the course of that inspection, the Signatory Attorney General will provide a list of those documents to Pfizer.

6.3 The State may assert any claim that Pfizer has violated this Judgment in a separate civil action to enforce compliance with this Judgment, or may seek any other relief afforded by law, but only after providing Pfizer an opportunity to respond to the notification described in paragraph 6.1 above; provided, however, that a Signatory Attorney General may take any action if the Signatory Attorney General concludes that, because of the specific practice, a threat to the health or safety of the public requires immediate action.

7. GENERAL PROVISIONS

7.1 Pfizer shall not cause or encourage third parties, nor knowingly permit third parties acting on its behalf, to engage in practices from which Pfizer is prohibited by this Judgment.

7.2 The acceptance of this Judgment by the Kansas Attorney General shall not be deemed approval by the Kansas Attorney General of any of Pfizer's advertising or business practices. Further, neither Pfizer nor anyone acting on its behalf shall state or imply, or cause to be stated or implied, that the Kansas Attorney General or any other governmental unit of the State of Kansas has approved, sanctioned or authorized any practice, act, advertisement, or conduct of Pfizer.

7.3 Any failure by any party to this Judgment to insist upon the strict performance by any other party of any of the provisions of this Judgment shall not be deemed a waiver of any of the provisions of this Judgment, and such party, notwithstanding such failure, shall have the right thereafter to insist upon the specific performance of any and all of the provisions of this Judgment.

7.4 This Judgment represents the full and complete terms of the settlement entered into by the Parties hereto. In any action undertaken by the Parties, no prior versions of this Judgment and no prior versions of any of its terms that were not entered by the Court in this Judgment, may be introduced for any purpose whatsoever.

7.5 This Court retains jurisdiction of this Judgment and the Parties hereto for the purpose of enforcing and modifying this Judgment and for the purpose of granting such additional relief as may be necessary and appropriate.

7.6 This Judgment may be executed in counterparts, and a facsimile or .pdf signature shall be deemed to be, and shall have the same force and effect as, an original signature.

7.7 All Notices under this Order shall be provided to the following via email and Overnight Mail:

For Pfizer Inc:
Joshua S. Levy
ROPES & GRAY LLP
Prudential Tower, 800 Boylston Street
Boston, MA 02199-3600
joshua.levy@ropesgray.com

Gary F. Giampetruzzi
Vice President and Assistant General Counsel, Head of Government Investigations
Pfizer Inc.
150/2/04
150 East 42nd Street
New York, NY 10017
Gary.Giampetruzzi@Pfizer.com

For Office of the Kansas Attorney General:
Office of the Kansas Attorney General
Consumer Protection/Antitrust Division
c/o Meghan E. Stoppel
120 SW 10th Ave., 2nd Floor
Topeka, Kansas 66612-1597
Meghan.Stoppel@gmail.com

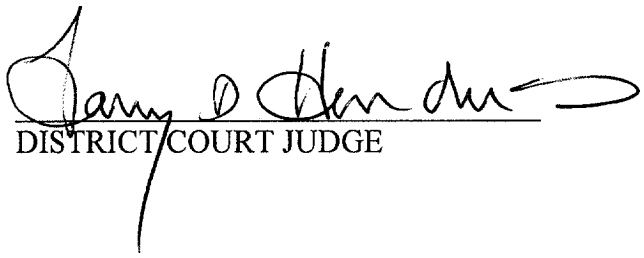
7.8 To the extent that any provision of this Judgment obligates Pfizer to change any policy(ies) or procedure(s) and to the extent not already accomplished, Pfizer shall implement the policy(ies) or procedure(s) as soon as reasonably practicable, but no later than 120 days after the Effective Date of this Judgment.

IT IS THEREFORE ORDERED, ADJUDGED AND DECREED that the stipulations and agreements of the Parties contained herein are adopted and approved as the findings of fact

and conclusions of law of the Court and any monies owed hereunder by Defendant immediately become a Judgment upon filing.

IT IS FURTHER ORDERED, ADJUDGED AND DECREED that pursuant to the Kansas Consumer Protection Act and the provisions of K.S.A. 50-632(b), the Court hereby approves the terms of this Judgment and adopts the same as the Order of the Court.

IT IS SO ORDERED.



DISTRICT COURT JUDGE

JOINTLY APPROVED AND
SUBMITTED FOR ENTRY:

FOR PLAINTIFF, STATE OF KANSAS

Derek Schmidt, KS #17781
Attorney General
Office of the Kansas Attorney General
120 SW 10th Ave., 2nd Floor
Topeka, Kansas 66612-1597
Phone: (785) 296-2215

Date: 12/10/2012

Meghan E. Stoppel, KS #23685
Assistant Attorney General
Office of the Kansas Attorney General
120 SW 10th Ave., 2nd Floor
Topeka, Kansas 66612-1597
Phone: (785) 296-3751
Fax: (785) 291-3699

Date: 12/10/12

FOR PFIZER INC

By: _____

Joshua S. Levy
Ropes & Gray LLP
Prudential Tower, 800 Boylston Street
Boston, MA 02199

Date: 12/5/12

By: _____

Ross B. Galin
O'Melveny & Myers LLP
Times Square Tower, 7 Times Square
New York, NY 10036

Date: 12/3/12

By: Mark S. Gunnison (as to form)

Mark S. Gunnison, KS # 11090
Payne & Jones Chtd.
11000 King St.
Overland Park, KS 66210

Date: 12/4/12

FOR PFIZER INC

By: _____ Date: 12/3/12

Gary F. Giampetruzzi
Vice President and Assistant General Counsel, Head of Government Investigations
Pfizer Inc
150/2/04
150 East 42nd Street
New York, NY 10017

Exhibit E

Meghan E. Stoppel, #23685
Assistant Attorney General
Office of the Kansas Attorney General
120 SW 10th Avenue, 2nd Floor
Topeka, Kansas 66612
Ph: (785) 296-3751
Fax: (785) 291-3699
meghan.stoppel@ag.ks.gov

FILED BY CLERK
K.S. DISTRICT COURT
THIRD JUDICIAL DIST.
TOPEKA, KS.

2014 AUG -6 A 11:44

IN THE DISTRICT COURT OF SHAWNEE COUNTY, KANSAS
Division 1

STATE OF KANSAS, *ex rel.*	)	
DEREK SCHMIDT, Attorney General,	)	
	)	
Plaintiff,	)	
	)	
v.	)	**Case No.** 2014 CV 777
	)	
WYETH	)	
PHARMACEUTICALS INC.,	)	
	)	
Defendant.	)	
	)	

(Pursuant to K.S.A. Chapter 60)

JOURNAL ENTRY OF CONSENT JUDGMENT

NOW on this 6 day of August, 2014, Plaintiff's Journal Entry of Consent Judgment comes before the Court pursuant to K.S.A. 50-632(b). The Plaintiff, State of Kansas, *ex rel.* Derek Schmidt, Attorney General, appears by and through Meghan E. Stoppel, Assistant Attorney General. Defendant Wyeth Pharmaceuticals Inc. (hereinafter "Wyeth") and Pfizer Inc ("Pfizer"), as current parent of Defendant Wyeth, appear by and through the undersigned counsel.

WHEREUPON the Parties advise the Court that they have stipulated and agreed to the following:

PARTIES, JURISDICTION AND VENUE

1. Derek Schmidt is the duly elected, qualified and acting Attorney General for the State of Kansas.

2. The Attorney General's authority to bring this action is derived from the statutory and common law of the State of Kansas, specifically the Kansas Consumer Protection Act, K.S.A. 50-623 *et seq.*

3. Venue is proper under K.S.A. 50-638 in the Third Judicial District of Kansas (Shawnee County).

4. At all times relevant hereto, Wyeth engaged in "consumer transactions" in Kansas, as defined by K.S.A. 50-624(c).

5. In October 2009, Pfizer Inc ("Pfizer") acquired Wyeth, and Wyeth became a wholly owned subsidiary of Pfizer. Pfizer represents that the conduct at issue occurred prior to this acquisition. Plaintiff, by its counsel, and Pfizer, by its counsel, have agreed to the entry of this Consent Judgment ("Judgment") by the Court without trial or adjudication of any issue of fact or law, and without finding or admission of wrongdoing or liability of any kind. Pfizer, as parent of Wyeth, agrees to be bound by the terms of this Judgment.

IT IS HEREBY ORDERED THAT:

1. FINDINGS

1.1 This Court has jurisdiction over the subject matter of this lawsuit and over all Parties, pursuant to the Kansas Consumer Protection Act, K.S.A. 50-623 *et seq*.

1.2 The terms of this Judgment shall be governed by the laws of the State of Kansas.

1.3 Entry of this Judgment is in the public interest and reflects a negotiated agreement among the Parties.

1.4 The Parties have agreed to resolve the issues resulting from the Covered Conduct by entering into this Judgment.

1.5 Pfizer is willing to enter into this Judgment regarding the Covered Conduct in order to resolve the Attorneys General's concerns under the State Consumer Protection Laws as to the matters addressed in this Judgment and thereby avoid significant expense, inconvenience, and uncertainty.

1.6 The Parties have agreed to resolve the issues raised by the Covered Conduct by entering into this Judgment.[1]

1.7 Pfizer is entering into this Judgment solely for the purpose of settlement, and nothing contained herein may be taken as or construed to be an admission or concession of any violation of law, rule, or regulation, or of any other matter of fact or law, or of any liability or wrongdoing, all of which Pfizer expressly denies. Pfizer does not admit any violation of the State Consumer Protection Laws set forth in footnote 6, and does not admit any wrongdoing that was or could have been alleged by any Attorney General before the date of the Judgment under those laws. No part of this Judgment, including its statements and commitments, shall constitute evidence of any liability, fault, or wrongdoing by Pfizer. This document and its contents are not intended for use by any third party for any purpose, including submission to any court for any purpose.

[1] This agreement is entered into pursuant to and subject to the State Consumer Protection laws cited in footnote 6.

1.8 This Judgment shall not be construed or used as a waiver or limitation of any defense otherwise available to Pfizer in any action, or of Pfizer's right to defend itself from, or make any arguments in, any private individual, regulatory, governmental, or class claims or suits relating to the subject matter or terms of this Judgment. This Judgment is made without trial or adjudication of any issue of fact or law or finding of liability of any kind. Notwithstanding the foregoing, a State may file an action to enforce the terms of this Judgment.

1.9 It is the intent of the Parties that this Judgment not be admissible in other cases or binding on Pfizer in any respect other than in connection with the enforcement of this Judgment.

1.10 No part of this Judgment shall create a private cause of action or confer any right to any third party for violation of any federal or state statute except that a State may file an action to enforce the terms of this Judgment.

1.11 This Judgment (or any portion thereof) shall in no way be construed to prohibit Pfizer from making representations with respect to any Pfizer Product that are required under Federal law or regulations or in Food and Drug Administration ("FDA") approved Labeling.

1.12 Nothing in this Judgment shall require Pfizer to:

(a) take any action that is prohibited by the Food, Drug and Cosmetic Act, 21 U.S.C. §301 *et seq.* ("FDCA") or any regulation promulgated thereunder, or by the FDA; or

(b) fail to take any action that is required by the FDCA or any regulation promulgated thereunder, or by the FDA. Any written or oral Promotional claim subject to this Judgment which is the same, or materially the same, as the language required or agreed to by the Director of the Office of Prescription Drug Promotion, the

Director of the Advertising and Promotional Labeling Branch, the Director of the Center for Drug Evaluation and Research, or the Director of the Center for Biologics Evaluation and Research, or their authorized designees in writing shall not constitute a violation of this Judgment, unless facts are or become known to Pfizer that cause the claim to be false, misleading, or deceptive.

2. DEFINITIONS

The following definitions shall be used in construing this Judgment:

2.1 "Clearly and Conspicuously" shall mean a disclosure in size, color, contrast, font, and location that is readily noticeable, readable and understandable and is presented in proximity to all information necessary to prevent it from being misleading or deceptive. A statement may not contradict or be inconsistent with any other information with which it is presented. If a statement modifies, explains, or clarifies other information or is necessary to prevent other information from being misleading or deceptive, then the statement must be presented in close proximity to that information, in a manner that is readily noticeable, readable, and understandable, and it must not be obscured in any manner.

2.2 "Covered Conduct" shall mean Wyeth's Promotional and marketing practices, and dissemination of information and remuneration to HCPs regarding the prescription drug Rapamune® through the Effective Date of the Judgment.

2.3 "Effective Date" shall mean the date on which a copy of this Judgment, duly executed by Pfizer and by the Signatory Attorney General, is approved by, and becomes a Judgment of the Court.

2.4 "FDA Guidances for Industry" shall mean final documents issued by the FDA pursuant to 21 U.S.C. §371(h) that represent the FDA's current thinking on a topic.

2.5 "Health Care Professional" or "HCP" shall mean any physician or other health care practitioner, who is licensed to provide health care services or to prescribe pharmaceutical products.

2.6 "Healthcare Organization" shall mean an entity, public or private, that is intended and incentivized to tie patient care to quality metrics and value models and includes organizations such as payors, Health Maintenance Organizations (HMO), Long Term Care (LTC) pharmacy providers, Pharmacy Benefit Management (PBM), Integrated Delivery Networks (IDN), Accountable Care Organizations (ACO), and hospital formulary committees.

2.7 "Labeling" shall mean all FDA-approved labels and other written, printed, or graphic matter (a) upon any article or any of its containers or wrappers, or (b) accompanying such article.

2.8 "Medical Information Response" shall mean a non-Promotional, scientific communication to address Unsolicited Requests for medical information from HCPs.

2.9 "Medical Outcome Specialists" shall mean Pfizer personnel who work with Healthcare Organizations that determine the drugs to be placed on a formulary.

2.10 "Multistate Executive Committee" shall mean the Attorneys General and their staffs representing California, Florida, Illinois, Maryland, New York, North Carolina, Oregon, Pennsylvania, and Texas.

2.11 "Multistate Working Group" shall mean the Attorneys General and their staff representing Alabama, Arizona, Arkansas, California, Colorado, Delaware, District of Columbia,

Florida, Georgia[2], Hawaii[3], Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Dakota, Tennessee, Texas, Utah[4], Virginia, Washington, and Wisconsin.

2.12 "Off-Label" shall mean a use related to an indication that was not approved by the FDA or information that was not contained in the FDA label at the time information regarding such use was communicated.

2.13 "Parties" shall mean Wyeth, Pfizer, and the Signatory Attorney General.

2.14 "Pfizer" shall mean Pfizer Inc and its wholly owned subsidiary, Wyeth Pharmaceuticals Inc., including all of its subsidiaries and divisions, predecessors, successors, and assigns doing business in the United States.

2.15 "Pfizer Marketing" shall mean Pfizer personnel responsible for marketing Rapamune in the United States.

2.16 "Pfizer Medical" shall mean Pfizer personnel assigned to the Pfizer medical organization, including those personnel assigned to Pfizer's Medication Information Department ("USMI") or any successor group performing the same functions as the USMI.

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[2] With regard to Georgia, the Administrator of the Fair Business Practices Act, appointed pursuant to O.C.G.A. § 10-1-395, is statutorily authorized to undertake consumer protection functions for the State of Georgia. References to the "States," "Parties," or "Attorneys General," with respect to Georgia, include the Administrator of the Fair Business Practices Act.

[3] Hawaii is being represented on this matter by its Office of Consumer Protection, an agency which is not part of the state Attorney General's Office, but which is statutorily authorized to undertake consumer protection functions, including legal representation of the State of Hawaii. For simplicity, the entire group will be referred to as the "Attorneys General," and such designation, as it includes Hawaii, refers to the Executive Director of the State of Hawaii Office of Consumer Protection.

[4] With regard to Utah, the Utah Division of Consumer Protection is charged with administering and enforcing the Consumer Sales Practices Act, the statute relevant to this judgment. References to the "States," "Parties," or "Attorneys General," with respect to Utah, refers to the Utah Division of Consumer Protection.

2.17 "Pfizer Product" or "Product" shall mean any FDA-approved prescription drug or biological product manufactured, distributed, sold, marketed or Promoted by Pfizer in the United States.

2.18 "Pfizer Sales" shall mean the Pfizer sales force, if any, responsible for United States Rapamune sales, including, but not limited to, the field force and all management personnel such as district managers, regional managers, vice president(s) over sales, and president over sales.[5]

2.19 "Promotional," "Promoting," or "Promote" shall mean representations about a Pfizer Product and other practices intended to increase sales or that attempt to influence prescribing practices of HCPs, including direct-to-consumer.

2.20 "Promotional Materials" shall mean any item used to Promote Rapamune.

2.21 "Promotional Media" shall mean Promotional Materials in any media format for use in speaker programs.

2.22 "Promotional Speaker" shall mean an HCP speaker engaged by Pfizer to Promote Rapamune.

2.23 "Rapamune" shall mean all Pfizer immunosuppressant Products that contain sirolimus or any other Pfizer Product that is currently approved by the FDA as prophylactic for solid organ rejection after transplant surgery.

2.24 "Reprints Containing Off-Label Information" shall mean articles or reprints from a scientific or medical journal, as defined in 21 C.F.R. 99.3(j), or reference publication, as defined in 21 C.F.R. 99.3(i), describing an Off-Label use of Rapamune.

[5] Pfizer represents that in January 2011, Pfizer withdrew the sales force responsible for marketing Rapamune®.

2.25 "Signatory Attorney General" shall mean the Attorney General of Kansas, or his/her authorized designee, who has agreed to this Judgment.

2.26 "State Consumer Protection Laws" shall mean the consumer protection laws cited in footnote 6 under which the Attorneys General have conducted the investigation.[6]

2.27 "Unsolicited Request" shall mean a request for information regarding Rapamune communicated to an agent of Pfizer that has not been prompted by or on behalf of Pfizer.

2.28 "Wyeth" shall mean Wyeth Pharmaceuticals Inc., a wholly owned subsidiary of Pfizer Inc.

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[6] ALABAMA – Alabama Deceptive Trade Practices Act § 8-19-1 *et seq.* (2002); ARIZONA - Consumer Fraud Act, A.R.S. §44-1521 et seq.; ARKANSAS – Arkansas Deceptive Trade Practices Act, Ark. Code Ann. § 4-88-101, et seq.; CALIFORNIA – Bus. & Prof Code §§ 17200 et seq. and 17500 et seq.; COLORADO – Colorado Consumer Protection Act, Colo. Rev. Stat. § 6-1-101 et seq.; DELAWARE – Delaware Consumer Fraud Act, Del. CODE ANN. tit. 6, §§ 2511 to 2527; DISTRICT OF COLUMBIA, District of Columbia Consumer Protection Procedures Act, D.C. Code §§ 28-3901 et seq.; FLORIDA – Florida Deceptive and Unfair Trade Practices Act, Part II, Chapter 501, Florida Statutes, 501.201 et. seq.; GEORGIA - Fair Business Practices Act, O.C.G.A. Sections 10-1-390 et seq.; HAWAII – Uniform Deceptive Trade Practice Act, Haw. Rev. Stat. Chpt. 481A and Haw. Rev. Stat. Chpt. 480; ILLINOIS – Consumer Fraud and Deceptive Business Practices Act, 815 ILCS 505/2 et seq.; INDIANA - Ind. Code §§ 24-5-0.5-0.1 et seq.; IOWA - Iowa Consumer Fraud Act, Iowa Code Section 714.16; KANSAS - Kansas Consumer Protection Act, K.S.A. 50-623 et seq.; KENTUCKY – Kentucky Consumer Protection Act, KRS Ch. 367.110, et seq.; LOUISIANA – Unfair Trade-Practices and Consumer Protection Law, LSA-R.S. 51:1401, et seq.; MAINE – Unfair Trade Practices Act, 5 M.R.S.A. § 207 et seq.; MARYLAND - Maryland Consumer Protection Act, Md. Code Ann., Com. Law §§ 13-101 et seq.; MASSACHUSETTS – Mass. Gen. Laws c. 93A, §§ 2 and 4; MICHIGAN – Michigan Consumer Protection Act, MCL § 445.901 et seq.; MINNESOTA - Minnesota Deceptive Trade Practices Act, Minn. Stat. §§ 325D.43-48; Minnesota False Advertising Act, Minn. Stat. § 325F.67; Minnesota Consumer Fraud Act, Minn. Stat. §§ 325F.68-70; Minnesota Deceptive Trade Practices Against Senior Citizens or Disabled Persons Act, Minn. Stat. § 325F.71.; MISSISSIPPI - Mississippi Consumer Protection Act, Miss. Code Ann.§ 75-24-1, et seq.; MISSOURI – Missouri Merchandising Practices Act, Mo. Rev. Stat. §§ 407.010 et seq.; NEBRASKA – Consumer Protection Act, Neb. Rev. Stat. §§ 59-1601 et seq. and Uniform Deceptive Trade Practices Act, Neb. Rev. Stat. §§ 87-301 et seq.; NEVADA – Deceptive Trade Practices Act, Nevada Revised Statutes 598.0903 et seq.; NEW HAMPSHIRE - New Hampshire Consumer Protection Act, RSA 358-A; NEW JERSEY – New Jersey Consumer Fraud Act, NJSA 56:8-1 et seq.; NEW MEXICO – NMSA 1978, § 57-12-1 et seq.; NEW YORK – General Business Law Art. 22-A, §§ 349-50, and Executive Law § 63(12); NORTH CAROLINA – North Carolina Unfair and Deceptive Trade Practices Act, N.C.G.S. 75-1.1, et seq.; NORTH DAKOTA – Unlawful Sales or Advertising Practices, N.D. Cent. Code § 51-15-02 et seq.; OHIO – Ohio Consumer Sales Practices Act, R.C. 1345.01, et seq.; OKLAHOMA – Oklahoma Consumer Protection Act 15 O.S. §§ 751 et seq.; OREGON – Oregon Unlawful Trade Practices Act, Or. Rev. Stat. § 646.605 et seq.; PENNSYLVANIA – Pennsylvania Unfair Trade Practices and Consumer Protection Law, 73 P.S. 201-1 et seq.; SOUTH DAKOTA – South Dakota Deceptive Trade Practices and Consumer Protection, SDCL ch. 37-24; TENNESSEE – Tennessee Consumer Protection Act, Tenn. Code Ann. 47-18-101 et seq.; TEXAS – Texas Deceptive Trade Practices-Consumer Protection Act, Tex. Bus. And Com. Code 17.41, et seq.; UTAH - Consumer Sales Practices Act, Utah Code Ann. §§ 13-11-1 et seq.; VIRGINIA-Virginia Consumer Protection Act, Va Code Ann. §59.1-196 et seq.; WASHINGTON – Unfair Business Practices/Consumer Protection Act, RCW §§ 19.86 et seq.; WISCONSIN – Wis. Stat. § 100.182 et seq. (Fraudulent Drug Advertising Representations).

2.29 Any reference to a written document shall mean a physical paper copy of the document, an electronic version of the document, or electronic access to such document.

3. COMPLIANCE PROVISIONS

IT IS FURTHER ORDERED, ADJUDGED AND DECREED THAT:

Promotional Activities

3.1 Pfizer shall not make, or cause to be made, any written or oral claim that is false, misleading, or deceptive regarding any Pfizer Product.

3.2 Pfizer shall not make any claim comparing the safety or efficacy of a Pfizer Product to another product when that claim is not supported by substantial evidence as defined by Federal law and regulations.

3.3 Pfizer shall not Promote Rapamune to an HCP who practices in a specialty that is unlikely to prescribe for a use in Rapamune's FDA approved Labeling.

3.4 Pfizer shall not make any written or oral Promotional claim of safety or effectiveness for any Pfizer Product in a manner that violates the FDCA, accompanying regulations, or voluntary agreements with FDA, as interpreted by the FDA in a writing by the Director of the Center for Drug Evaluation at the FDA.

3.5 Pfizer shall not Promote any Pfizer Product for Off-Label uses.

3.6 Pfizer shall not make any claim that contradicts or minimizes a precaution, warning, or adverse reaction that is described in product Labeling for Rapamune.

3.7 In Promotional Materials, Pfizer shall Clearly and Conspicuously disclose all material facts regarding the following: the risks associated with Rapamune as set forth in the products' FDA-approved Labeling; information in any boxed warning; and facts about the

negative consequences and side effects that can result from use of Rapamune. Pfizer shall present information about effectiveness and risk in a balanced manner. Whenever Pfizer knows or has reason to believe the current Labeling does not reflect the efficacy or risks of Rapamune, Pfizer shall promptly notify the Food and Drug Administration.

3.8 Pfizer shall not affirmatively seek the inclusion of Rapamune in hospital protocols or standing orders unless Rapamune has been approved by the FDA for the indication for which it is to be included in the protocol or standing order.

3.9 Pfizer shall require that all Promotional Speakers comply with Pfizer's obligations in paragraphs 3.1 through 3.8, 3.24, and 3.28 of this Judgment, including, but not limited to, ensuring that all Promotional Speakers' Promotional Materials and Promotional Media for Rapamune comply with Pfizer's obligations in this Judgment.

3.10 Pfizer shall notify its sales force promptly of any warning letter received from the FDA which affects the conduct of any sales representative in Promoting the relevant Pfizer Product and shall promptly provide a detailed explanation of the effect of the letter on the Promotion of Pfizer Products.

Financial Incentives to Pfizer Sales, Medical Outcome Specialists, and/or Pfizer Marketing

3.11 Pfizer's financial incentives shall be designed to ensure that Pfizer Sales, Medical Outcome Specialists, and/or Pfizer Marketing are not motivated to engage in improper Promoting, selling, and marketing of Rapamune.

3.12 Pfizer's financial incentives shall not include mechanisms to provide incentive compensation for sales that may be attributable to the Off-Label uses of any Pfizer Product.

3.13 For six years from the Effective Date of this Judgment, Pfizer shall continue to implement measures whereby sales goals, if any, for Rapamune can be met without including Off-Label prescriptions.

Dissemination and Exchange of Medical Information

The following provisions shall be effective for six years from the Effective Date of this Judgment.

3.14 Pfizer shall not knowingly disseminate any Medical Information Response, including one that describes any Off-Label use of Rapamune, that makes any false, misleading, or deceptive representation regarding Rapamune or any false, misleading, or deceptive statement concerning a competing product.

3.15 Pfizer Sales, Pfizer Marketing, and Medical Outcomes Specialists shall not develop the medical content of Medical Information Responses regarding Rapamune. Notwithstanding the foregoing, Medical Outcomes Specialists may assist in the development of pharmacoeconomic content of Medical Information Responses.

3.16 Medical Information Responses to Unsolicited Requests for Off-Label information regarding Rapamune may be disseminated only by Pfizer Medical.

3.17 Pfizer Medical shall have ultimate responsibility for developing and approving all Medical Information Responses regarding Rapamune. Additional approvals may be provided by Pfizer's legal department. Pfizer shall not distribute any such materials unless:

(a) clinically relevant information is included in these materials to provide scientific balance;

(b) data in these materials are presented in an unbiased, non-Promotional manner; and

(c) these materials are clearly distinguishable from sales aids and other Promotional Materials.

Responses to Unsolicited Requests for Off-Label Information

The following provisions shall be effective for six years from the Effective Date of this Judgment.

3.18 If Pfizer elects to respond to an Unsolicited Request for Off-Label information Pfizer Medical shall provide specific, accurate, objective, and scientifically balanced responses. Any such response shall not Promote Rapamune for any Off-Label use(s).

3.19 Any written Pfizer response to an Unsolicited Request for Off-Label information regarding Rapamune shall be a Medical Information Response and shall include:

(a) a copy of the FDA-required Labeling, if any, for the product (e.g., FDA- approved package insert and, if the response is for a consumer, FDA-approved patient labeling);

(b) a prominent statement notifying the recipient that the FDA has not approved or cleared the product as safe and effective for the Off-Label use addressed in the accompanying materials;

(c) a prominent statement disclosing the indication(s) for which FDA has approved or cleared the product;

(d) a prominent statement providing all important safety information including, if applicable, any boxed warning for the product;

(e) non-biased information or data relating to the particular Off-Label use that is the subject of the request, including applicable data that are not supportive or that cast doubt on the safety or efficacy of that use; and

(f) a comprehensive list of references for all of the information disseminated in the response (e.g., a bibliography of publications in peer-reviewed medical journals or in medical or scientific texts; citations for data on file, for summary documents, or for abstracts).

3.20 Pfizer Sales, Pfizer Marketing, and Medical Outcome Specialists may respond orally to an Unsolicited Request for Off-Label information regarding Rapamune only by offering to request on behalf of the HCP that a Medical Information Response be sent to the HCP in follow up or by offering to put the HCP in touch with Pfizer Medical. Notwithstanding the foregoing, Medical Outcomes Specialists may respond to inquiries related to pharmacoeconomics or health outcomes from formulary decision makers or the groups responsible for the management of health benefits within Healthcare Organizations, but not prescribers unless employed or engaged by a Healthcare Organization in a role connected to formulary decisions or the management of health benefits.

3.21 Information distributed by USMI in response to an Unsolicited Request for Off-Label information shall be:

(a) provided only to the individual making the request;

(b) tailored to answer only the specific Off-Label question(s) asked;

(c) scientific in nature; and

(d) unaccompanied by other material or information that is Promotional in nature or tone.

Reprints

3.22 Pfizer shall not disseminate any information describing any Off-Label use of any Pfizer Product if such use has been submitted to the FDA for approval and the FDA has either advised Pfizer that it refuses to approve such application or that FDA-identified deficiencies must be resolved before approval can be granted unless Pfizer has first Clearly and Conspicuously disclosed to the recipient of the information that the FDA has issued such advice. Pfizer may disclose to any recipient of such information whether the information was presented to the FDA prior to the FDA's issuance of such advice regarding the Off-Label use.

3.23 Pfizer shall not disseminate information describing any Off-Label or unapproved use of Rapamune unless such information and materials comply with applicable FDA regulations and the recommended actions in FDA Guidances for Industry.

Reprints Containing Off-Label Information

3.24 Pfizer Medical shall be responsible for the identification, selection, approval and dissemination of Reprints Containing Off-Label Information regarding Rapamune.

3.25 Reprints Containing Off-Label Information regarding Rapamune:

(a) shall be accompanied by the FDA approved Labeling for the product and contain a disclosure in a prominent location, which would include the first page or as a cover page where practicable, indicating that this article discusses Off-Label information; and

(b) shall not be referred to or used in a Promotional manner.

3.26 Reprints Containing Off-Label Information regarding Rapamune may only be disseminated by Pfizer Medical to HCPs. Notwithstanding the foregoing, Medical Outcomes Specialists may disseminate reprints relating to pharmacoeconomics or health outcomes to formulary decision makers or the groups responsible for the management of health benefits within Healthcare Organizations, but not prescribers unless employed or engaged by a Healthcare Organization in a role connected to formulary decisions or the management of health benefits.

3.27 Nothing in this Judgment shall preclude Pfizer from disseminating reprints which have only an incidental reference to Off-Label information. If reprints have an incidental reference to Off-Label information, such reprints shall not be subject to the requirements of Section 3.23 and such incidental reference to Off-Label information shall not be referred to or used in a Promotional manner as prohibited by Section 3.25(b).

3.28 Pfizer shall maintain a disclosure program which allows for the anonymous disclosure of compliance policy violations and contains a no retaliation policy.

Clinical Research

3.29 Pfizer shall report clinical research regarding Rapamune in an accurate, objective and balanced manner, and as required by applicable law. For all Pfizer-sponsored clinical trials and to the extent permitted by the National Library of Medicine, Pfizer shall register clinical trials and submit clinical trial results to the federal clinical trial registry and results data bank regarding Rapamune on the publicly accessible NIH website (www.clinicaltrials.gov) as required by the FDA Amendments Act of 2007, Public Law No. 110-85, 121 Stat 823, and any accompanying regulations that may be promulgated pursuant to that Act.

3.30 When presenting information about a clinical study regarding Rapamune in any Promotional materials, Pfizer shall not do any of the following:

(a) present information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions;

(b) use the concept of statistical significance to support a claim that has not been demonstrated to have clinical significance or validity or fails to reveal the range of variations around the cited average results;

(c) use statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from the study, the design or protocol of which is not amenable to formal statistical evaluations;

(d) present the information in a way that implies that the study represents larger or more general experience with the drug than it actually does;

(e) use statistics on numbers of patients, or counts of results or side effects, derived from pooling data from various insignificant or dissimilar studies in a way that suggests either that such statistics are valid if they are not or that they are derived from large or significant studies supporting favorable conclusions when such is not the case. If any results derived from pooling data are presented, Pfizer shall disclose the method of pooling;

(f) use tables or graphs to distort or misrepresent the relationships, trends, differences, or changes among the variables or products studied; or

(g) use reports or statements represented to be statistical analyses, interpretations, or evaluations that are inconsistent with or violate the established principles of statistical theory, methodology, applied practice and inference, or that are derived from clinical studies the design, data, or conduct of which substantially invalidate the application of statistical analyses, interpretation, or evaluation.

3.31 Pfizer shall not seek to influence the prescribing of Rapamune in hospitals or transplant centers in any manner (including through funding clinical trials) that does not comply with the Federal anti-kickback statute (codified at 42 U.S.C. § 1320a-7b).

4. PAYMENT

4.1 No later than 30 days after the Effective Date of this Judgment, Pfizer shall pay a total amount of Thirty-Five Million Dollars ($35,000,000.00) to be divided and paid by Pfizer directly to each Signatory Attorney General of the Multistate Working Group in an amount to be designated by and in the sole discretion of the Multistate Executive Committee. Said payment shall be used by the States as attorneys' fees and other costs of investigation and litigation, or to be placed in, or applied to, the consumer protection enforcement fund, including future consumer protection enforcement, consumer education, litigation or local consumer aid fund or revolving fund, used to defray the costs of the inquiry leading hereto, or for any lawful purpose, at the sole discretion of each Signatory Attorney General. The Parties acknowledge that the payment described herein is not a fine, penalty, or payment in lieu thereof.

5. RELEASE

5.1 By its execution of this Judgment, the State of Kansas releases Pfizer and all of its past and present, subsidiaries and divisions, predecessors, successors, and assigns (collectively,

the "Released Parties") from the following: all civil claims, causes of action, damages, restitution, fines, costs, and penalties that the Kansas Attorney General has asserted or could have asserted against the Released Parties under the above-cited consumer protection statutes resulting from the Covered Conduct up to and including the Effective Date.

5.2 Notwithstanding any term of this Judgment, specifically reserved and excluded from the release in Paragraph 5.1 as to any entity or person, including Released Parties, are any and all of the following:

(a) any criminal liability that any person and/or entity, including Released Parties, has or may have to the State of Kansas.

(b) any civil or administrative liability that any person and/or entity, including Released Parties, has or may have to the State of Kansas not expressly covered by the release in Paragraph 5.1 above, including, but not limited to, any and all of the following claims:

(i) state or federal antitrust violations;

(ii) claims involving "best price," "average wholesale price," "wholesale acquisition cost," or any reporting practices;

(iii) Medicaid claims, including, but not limited to, federal Medicaid drug rebate statute violations, Medicaid fraud or abuse, and/or kickback violations related to any State's Medicaid program;

(iv) state false claims violations; and

(v) actions of state program payors of the State of Kansas arising from the purchase of a Pfizer Product.

(c) any liability under the State of Kansas's above-cited consumer protection laws which any person and/or entity, including Released Parties, has or may have to individual consumers.

5.3 Nothing contained in this Judgment shall relieve Pfizer of the obligations it maintains under any other Judgment or agreement relating to any Pfizer Product.

6. DISPUTE RESOLUTION

6.1 For the purposes of resolving disputes with respect to compliance with this Judgment, should any of the Signatory Attorneys General have a reasonable basis to believe that Pfizer has engaged in a practice that violates a provision of this Judgment subsequent to the Effective Date of this Judgment, then such Attorney General shall notify Pfizer in writing of the specific objection, identify with particularity the provision of this Judgment that the practice appears to violate, and give Pfizer thirty (30) days to respond to the notification; provided, however, that a Signatory Attorney General may take any action if the Signatory Attorney General concludes that, because of the specific practice, a threat to the health or safety of the public requires immediate action. Upon receipt of written notice, Pfizer shall provide a good-faith written response to the Attorney General notification, containing either a statement explaining why Pfizer believes it is in compliance with the Judgment, or a detailed explanation of how the alleged violation occurred and a statement explaining how Pfizer intends to remedy the alleged breach. Nothing in this section shall be interpreted to limit the state's Civil Investigative Demand ("CID") or investigative subpoena authority, to the extent such authority exists under applicable law, and Pfizer reserves all of its rights in responding to a CID or investigative subpoena issued pursuant to such authority.

6.2 Upon giving Pfizer thirty (30) days to respond to the notification described above, the Signatory Attorney General shall also be permitted reasonable access to inspect and copy relevant, non-privileged, non-work product records and documents in the possession, custody, or control of Pfizer that relate to Pfizer's compliance with each provision of this Judgment pursuant to that State's CID or investigative subpoena authority. If the Signatory Attorney General makes or requests copies of any documents during the course of that inspection, the Signatory Attorney General will provide a list of those documents to Pfizer.

6.3 The State may assert any claim that Pfizer has violated this Judgment in a separate civil action to enforce compliance with this Judgment, or may seek any other relief afforded by law, but only after providing Pfizer an opportunity to respond to the notification described in paragraph 6.1 above; provided, however, that a Signatory Attorney General may take any action if the Signatory Attorney General concludes that, because of the specific practice, a threat to the health or safety of the public requires immediate action.

7. GENERAL PROVISIONS

7.1 Pfizer shall not cause or encourage third parties, nor knowingly permit third parties acting on its behalf, to engage in practices from which Pfizer is prohibited by this Judgment.

7.2 The acceptance of this Judgment by the Kansas Attorney General shall not be deemed approval by the Kansas Attorney General of any of Pfizer's advertising or business practices. Further, neither Pfizer nor anyone acting on its behalf shall state or imply, or cause to be stated or implied, that the Kansas Attorney General or any other governmental unit of the

State of Kansas has approved, sanctioned or authorized any practice, act, advertisement, or conduct of Pfizer.

7.3 Any failure by any party to this Judgment to insist upon the strict performance by any other party of any of the provisions of this Judgment shall not be deemed a waiver of any of the provisions of this Judgment, and such party, notwithstanding such failure, shall have the right thereafter to insist upon the specific performance of any and all of the provisions of this Judgment.

7.4 This Judgment represents the full and complete terms of the settlement entered into by the Parties hereto. In any action undertaken by the Parties, no prior versions of this Judgment and no prior versions of any of its terms that were not entered by the Court in this Judgment, may be introduced for any purpose whatsoever.

7.5 This Court retains jurisdiction of this Judgment and the Parties hereto for the purpose of enforcing and modifying this Judgment and for the purpose of granting such additional relief as may be necessary and appropriate.

7.6 This Judgment may be executed in counterparts, and a facsimile or .pdf signature shall be deemed to be, and shall have the same force and effect as, an original signature.

7.7 All Notices under this Judgment shall be provided to the following via email and Overnight Mail:

For Pfizer Inc:
Joshua S. Levy
ROPES & GRAY LLP
Prudential Tower, 800 Boylston Street
Boston, MA 02199-3600
joshua.levy@ropesgray.com

Margaret M. Madden
Vice President and Assistant General Counsel
Pfizer Inc
235 East 42nd Street
New York, NY 10017
margaret.m.madden@Pfizer.com

For Office of the Kansas Attorney General:
Office of the Kansas Attorney General
Consumer Protection/Antitrust Division
c/o Meghan E. Stoppel
120 SW 10th Ave., 2nd Floor
Topeka, Kansas 66612-1597
meghan.stoppel@ag.ks.gov

7.8 To the extent that any provision of this Judgment obligates Pfizer to change any policy(ies) or procedure(s) and to the extent not already accomplished, Pfizer shall implement the policy(ies) or procedure(s) as soon as reasonably practicable, but no later than 120 days after the Effective Date of this Judgment.

IT IS THEREFORE ORDERED, ADJUDGED AND DECREED that the stipulations and agreements of the Parties contained herein are adopted and approved as the findings of fact and conclusions of law of the Court and any monies owed hereunder by Defendant immediately become a Judgment upon filing.

IT IS FURTHER ORDERED, ADJUDGED AND DECREED that pursuant to the Kansas Consumer Protection Act and the provisions of K.S.A. 50-632(b), the Court hereby approves the terms of this Judgment and adopts the same as the Order of the Court.

IT IS SO ORDERED.

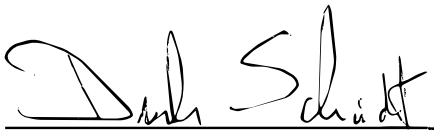
DISTRICT COURT JUDGE

SEAL of the DISTRICT COURT SHAWNEE CO. KANSAS

STATE OF KANSAS, COUNTY OF SHAWNEE, S.S.
I hereby certify the above and foregoing to be a true and correct copy, the original of which is filed and entered of record in the court.
Dated August 6, 2014
CLERK of the DISTRICT COURT
By Amy Michaelis DEPUTY

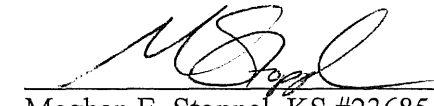
JOINTLY APPROVED AND
SUBMITTED FOR ENTRY:

FOR PLAINTIFF, STATE OF KANSAS



Date: 8/6/2014

Derek Schmidt, KS #17781
Attorney General
Office of the Kansas Attorney General
120 SW 10th Ave., 2nd Floor
Topeka, Kansas 66612-1597
Phone: (785) 296-2215



Date: 8/6/14

Meghan E. Stoppel, KS #23685
Assistant Attorney General
Office of the Kansas Attorney General
120 SW 10th Ave., 2nd Floor
Topeka, Kansas 66612-1597
Phone: (785) 296-3751
Fax: (785) 291-3699

FOR PFIZER INC

By: _____ Date: 7/31/14

Margaret M. Madden
Vice President and Assistant General Counsel
Pfizer Inc

FOR WYETH PHARMACEUTICALS INC.

By: _____ Date: 7/31/14

Margaret M. Madden
Vice President and Assistant General Counsel
Pfizer Inc

FOR PFIZER INC & WYETH PHARMACEUTICALS INC.

By: _____ Date: 8-1-14

Joshua S. Levy
Ropes & Gray LLP
Prudential Tower, 800 Boylston Street
Boston, MA 02199

LOCAL COUNSEL FOR PFIZER INC & WYETH PHARMACEUTICALS INC.

By: Taylor Fields Date: 8/1/14

Taylor Fields, KS# 77913
Fields & Brown, LLC
1100 Main, Suite 1600
Kansas City, Missouri 64105
Phone: (816) 474-1700
Fax: (816)421-6239
tfields@fieldsandbrown.com

4.

TESTIMONIES
OF
MEDICAL AUTHORITIES
ON
VACCINATION.

WITH INDEX, DISTINGUISHING BY AN ASTERISK SUCH AS TREAT OF ANIMAL (COW, HORSE, OR CALF) LYMPH, WITHOUT REFERENCE TO ARM TO ARM VACCINATION.

DR. BARON, in his Life of Jenner, vol. 1. page 243, says, "that matter from the pustules of the vaccinated she-ass, affords the genuine cow-pox in man." But the great JOHN HUNTER says, "The introduction by inoculation of mineral or vegetable poisons into the blood, is hazardous, and in certain quantities may be destructive; *but the introduction of animal products from another living body, be it a man, a cow, or even an ass, is infinitely more pernicious, because allied to it in being vitalised.*"

The propagation of disease, on the pretext of thereby arresting disease, is bad in logic, wicked in morals, and futile in practice. Then, again, the testimony of the greatest authority in the world ought to be allowed to silence nobody. Intelligent persons have as much title as they to respectful consideration. We have no prelacy in science. It is easy to deal in epithets, to call those insane who differ with us, but no gentleman, nor friend of truth and honorable dealing, does it. We waive the fact that the flagrant terms of this blackguard logic apply to such men as PROF. NEWMAN, PROF. ENNEMOSER, JOHN HUNTER, and ALEXANDER VON HUMBOLDT. He may as well throw his filth at them as at anybody else. It does not prove that vaccine virus, being the product of animal decay, it is innocent to infuse it into healthy persons' blood. Vaccination is but a charlatan device, born of empiricism, and without a sound leg to stand on. Well-educated pathologists know this. —*New York Medical Tribune*, 1881.

———:o:———

LONDON SOCIETY FOR THE ABOLITION OF COMPULSORY VACCINATION,

114, VICTORIA STREET, WESTMINSTER, S.W.

———:o:———

Price Three-Pence, or Eighteen Shillings per Hundred.

GEORGE GREGORY,
Book Merchant and Library Buyer,
5, Argyle Street, BATH.

PREFACE.

THE opposition to compulsory vaccination is based mainly upon two propositions. First, that vaccination, which was claimed by JENNER and his immediate followers to afford immunity from small-pox for life, does not afford immunity either for life, or for any portion of life, and secondly, that the operation is always attended with danger, and is sometimes fatal. The first proposition formed the subject of the tract issued by the LONDON SOCIETY FOR THE ABOLITION OF COMPULSORY VACCINATION, entitled: "*Testimonies of Medical Men on the Protection Supposed to be Afforded by Vaccination, from* 1805 *to* 1881." These testimonies demonstrate that the failures of vaccination to protect were coincident with the introduction of the JENNERIAN rite, and it is no longer denied that numerous cases of small-pox were discovered amongst patients who had received virus from JENNER'S own lancet. MR. WHITE has shewn in his "Story of a Great Delusion," published in the pages of the "*Vaccination Inquirer and Health Review*," the subterfuges which were resorted to for concealing, denying, and explaining away these oft-recurring examples of post-vaccinal small-pox, JENNER himself giving the *mot d'ordre* to his professional brethren "to be slow in publishing such cases." The second proposition, that vaccination is the means of introducing serious disorders into the human system, is treated of in the following pages, which consist solely of evidence furnished by members of the profession. Some of these testimonies have been reluctantly tendered by believers in the protective efficacy of the operation. Others are avowals by heads of small-pox hospitals, medical

practitioners at childrens' hospitals, public vaccinators, medical officers of health, and general practitioners; the admitted results of a large experience, which they could no longer conscientiously withhold. The alleged unanimity of the faculty concerning vaccination is often quoted as an invincible argument in its favour, but many of these testimonies (which are only a few out of hundreds of others of like character before us) prove that this claim is utterly opposed to the truth. By adroitly concealing their conflicting opinions from the public, the medical faculty gains the advantage of a unanimity which is apparent but not real. Medical Journals as a rule refuse all criticism of orthodox theories, and the exclusion is most rigidly enforced against the opponents of the state-endowed preservative. Indeed, the conduct of the press on the vaccination question goes beyond prejudice and rises into anger.

When MR. HIBBERT, M.P. for Oldham, the under-secretary to the Local Government Board, stated that the reason for introducing the Government Bill in 1880, for abolishing cumulative penalties, was the occurrence of cases of syphilitic contamination following vaccination, the "*Lancet*" gravely charged the Government with playing into the hands of the anti-vaccinators. And there can be little doubt, that if a tenth part of the cases of injury and death caused by vaccination were disclosed by the faculty, the whole superstructure would crumble under the weight of public indignation. What the faculty conceal, with a view, to use the words of MR. MAY, Medical Officer of Health, (see page 34,) "to save vaccination from reproach," the parliamentary returns disclose; and the following official figures shew the deadly results of this pernicious practice. The increase of infantile mortality from inoculable diseases, it will be seen, is concurrent with the more rigorous enforcement of the vaccination law.

Return No. 392, Sess. 2, 1880, made by the Registrar-General to the House of Commons, shewing the annual average death-rate of infants under one, per million of births, from five causes:—

syphilis, scrofula tabes (internal scrofula), skin diseases, phlegmon (boils), and pyæmia (blood-poisoning), also from the causes of bronchitis and diarrhœa during the septemial periods under-mentioned.

Average Annual Proportion (7 Years) per Million of Births.	*Syphilis.*	*Scrofula.*	*Tabes Mesenterica.*	*Skin Disease.*	*Phlegmon and Pyæmia.*	*Aggregate. 5 causes Inoculable.*	*Bronchitis.*	*Diarrhœa.*	*Two other causes apparently Vaccinal.*
1847-53. Prior to Vaccine Legislation.	564	351	2981	168	207	4271	5101	11599	16700
1854-60. Vaccination made Compulsory, /53.	998	496	3191	233	318	5036	7666	13002	20668
1861-67. Compulsion more Stringent, /67.	1416	727	3580	273	165	6161	9956	12298	22254
1868-74. More Legislation, /71.	1720	827	4225	302	153	7227	12937	18867	31804
1875-78. The last given (four years).	1801	1050	4632	415	227	7898	16958	15951	32909

The annual average increase from the five causes which are directly inoculable, and may therefore be produced by vaccination, is 3627 per million of births—and from the two indirect causes, 16209—or 20000 together, concurrently with enforced vaccination under three months old. The inclusion of children above one year might multiply the result.

Dr. Charles Pigeon, of Fourchambault, France, maintained at the Cologne International Anti-Vaccination Congress, that if doctors were made responsible for damages arising out of vaccination, they would refuse the risk, and the system would be speedily abandoned; otherwise the profession would be financially bankrupt.

The cases of injury arising from this medical prescription are now so common, that every practitioner of experience has seen them, and none will venture to deny their possibility. Hence the cry all along the line for fresh supplies of "*bovine virus*," "calf

lymph," or humanized virus with but few removes from the original heifer stock, whereby what SIR THOS. WATSON describes as the "ugly blot," may be extinguished. The alleged cow-pox in adult cattle, has always been a mystery to the farmer, and while its value has never been proved, its dangers have already been established. In opening the Vaccination Discussion at the Annual Meeting at Ryde, last August, the Chairman, MR. ERNEST HART, declared that a great change had come over the medical profession in respect to arm to arm vaccination. DR. WARLOMONT says, we must have a stock which, like Cæsar's wife, is above suspicion. The medical opinions here collected, will shew that the new demand is for an impossibility—there never has been such a vaccine virus. The poison was always poisonous, and one proof of the risks attending vaccination is the invariable refusal of medical men to take the responsibility of the operation. They know the peril, and wisely decline the risk; which they would accept, were it like taking a bath, or any other sanitary preservative against infection. A Railway Company which inadvertently injures or kills a passenger, and, under recent legislation, a manufacturer who inadvertently injures or kills an employé, incur legal liability. Why, then, should not the doctor who recommends an operation be held liable in like manner? The London College of Surgeons issued a report as early as 1806, before any genuine cow-pox virus could have had time to be contaminated with the results of a nation's vices, admitting bad consequences of vaccination in 66 cases of eruptions of the skin, and in 24 cases of inflammation of the arm, whereof 3 proved fatal. (See Page 11.)

Many of the testimonies which follow, refer to the dangerous results of animal virus by those who have tested it, and there is therefore no alternative but to abandon the practice altogether, which, alike in its original form and in its latest fashionable transmutation, is productive only of evil.

In the meantime, although the laws whenever possible are rigidly enforced, and the consciences of thousands of upright and honest citizens are coerced, the number of intelligent and unbending

recusants is daily on the increase. In the town of Leicester last year, there were 1229 prosecutions for non-vaccination, the popular instinct judiciously preferring the pains and penalties of the law without cow-pox, to the costly risks with it. In Keighley, according to the latest return issued by the Board of Guardians, no more than 12½ per cent. of the births are vaccinated, and yet we are told there has only been one case of small-pox for 5 years. How long will the constituencies connive at injustice, by continuing to send Members to Parliament, who persistently shut their eyes to the facts, and ignore the plain teachings of 80 years of vaccinal suffering and wholesale distribution of useless and unmerited disease, based on no scientific fact, and contributing no share in the lessening of the national death rate?—W. T.

London, *March*, 1882.

THE LONDON SOCIETY

FOR THE

Abolition of Compulsory Vaccination.

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II.—The Diffusion of Knowledge concerning Vaccination.
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MEDICAL TESTIMONIES.

* Dr. SQUIRRELL, of the London Small-Pox Hospital, a Contemporary of Jenner,

Opposed vaccination on the ground that we have already too many maladies ; that it affords no security against small pox ; and that it was frequently followed by injurious consequences, in support of which conclusions he instanced thirty-nine cases.

* Dr. PEARSON, 1799.

This intimate friend and coadjutor of Jenner, in a letter to him, describes the eruptions in the vaccinated patients in London. "You will be astonished at my talking of eruptions, but it now appears in Dr. Woodville's cases, that as many have eruptions on the body as have them only in the parts inoculated. I inoculated an infant yesterday in Dr. Woodville's presence, from a patient ill of the cow-pox with eruptions on his body to the amount of two or three hundred . . . . On telling Dr. Woodville that I had been anxious about your publishing the use of the caustic, he replied, 'That would have damned the whole business.' Be assured that, if the practice [of vaccination] cannot be introduced without the caustic, it will never succeed with the public."—*Life of Jenner, by Baron*, i. 313, 315.

* JOHN BIRCH, Surgeon Extraordinary to the Prince of Wales, and Surgeon to St. Thomas's Hospital, 1804-7.

I have thought it a duty to publish my answer to the questions of the College of Surgeons, and my letter to the College of Physicians. In the last of these I have adduced no less than seven cases of death caused by vaccination. I could add more, but the cases adduced are enough to refute the assertions made to the House of Commons, that vaccination might be safely adopted because it was *never fatal.*

I have known several bad effects occur in consequence of vaccination. The case of Rebecca Latchford is published: spring and fall she is usually visited with some eruption or suppuration about the face or arm. I have also seen more than two cases similar to that of Jowles, in which the face has been principally attacked. By some vaccinators these eruptions are called scrofula : but how can this be reconciled with the positive assurance of a justly celebrated surgeon, on which parliament

relied ; that neither scrofula, nor any other disease, was excited by vaccination.

Besides the singular eruptions above mentioned, I have seen many others of a very itching nature, and some shrivelled scaly skins consequent on cow-pox.

CAPTAIN BUTTS, of the Navy, lost an infant from an eruption which took place immediately from the affection of the arm.

I have information from Hertford of five cases of small-pox occurring after vaccination, in four of which the patients died.

In Lambeth Workhouse several died of small-pox subsequent to vaccination.

In respect of the consequences of vaccination I am compelled to declare, that I see new and anomalous eruptions following this disease ; eruptions, which in the whole course of my former practice I never met with, and which I must conscientiously refer to this novel practice.

MR. BIRCH concludes as the result of observation and experience :

1. That cow-pox has in more than one instance proved fatal.

2. That cow-pox is productive of new appearances of disease, unknown before in the catalogue of human impurities.

3. That cow-pox is not by any means to be depended on as a security against the natural small-pox.

*EXTRACT FROM THE REPORT OF THE FIRST VACCINE INSTITUTION :

"It is our duty to acknowledge that four or five cases have proved fatal from the affection of the part vaccinated."

*DR. LETTSOM, 1805,

Was one of JENNER'S coadjutors in introducing the cow-pox. A friend of DR. LETTSOM, writing in the *Gentleman's Magazine* for 1802, says :—" It has been disputed of the old inoculation, whether any other disease could be transmitted with the small-pox : DR. LETTSOM grants there may, which is a *serious* hazard."

*WILLIAM ROWLEY, a Member of the University of Oxford, and of the Royal College of Physicians in London ; Physician Extraordinary to Her Majesty's Lying-in-Hospital, 1805 ; Public Lecturer on the Theory and Practice of Medicine, &c.

In 1805, wrote :—It results from the general resumé of all these authentic facts, that out of 504 persons vaccinated in England, 75 died from the consequences, and almost all have had the small-

pox, some sooner, some later, after their vaccination. There is no question here of supposition or calculation of probability, *it is truth!* It is evidence which seems to speak and leaves no doubt. Now, if in the space of 7 or 8 years, (from 1798 to 1805,) vaccination has shown itself so grievous to society, what may we not fear for the future? It will scarcely be imagined that the facts mentioned are all that might be cited to prove the inefficiency and dangers of the practice. Alas! it is too certain that on all sides we meet with new instances of maladies such as those already detailed. Consider England, France, Germany, Italy, and other countries, where vaccination has been received; penetrate into the interior of houses, into the bosom of families; interrogate fathers and mothers, and you will be surprised, shocked, and even enraged to see, not only tolerated but maintained, a murderous practice, which carries desolation into families, and compromises the reputation of those who protect or practise it.

*LONDON COLLEGE OF SURGEONS, 1806.

Eleven hundred circulars were dispatched on 15th December, 1806, to all the members of the College whose addresses were known in the United Kingdom, submitting the following questions—

1st. How many persons have you vaccinated?

2nd. Have any of your patients had small-pox after vaccination;

3rd. Have any bad effects occurred in your experience in consequence of vaccination? and if so, what were they?

4th. Is the practice of vaccination increasing or decreasing in your neighbourhood? if decreasing, to what cause do you impute it?

To the 1100 circulars only 426 replies were received. Why nearly two-thirds of the members kept silent, when at the outset they were converted in multitudes to Vaccination, is left unexplained. The replies were thus summarised by the Board on 17th March, 1807—

The number of persons stated in such letters to have been vaccinated, is 164,381.

The number of cases in which small-pox had followed vaccination is 56.

The Board think it proper to remark under this head, that, in the enumeration of cases in which small-pox has succeeded vaccination, they have included none but those in which the subject was vaccinated by the surgeon reporting the facts.

The bad consequences which have arisen from vaccination are—

66 cases of eruption of the skin, and

24 of inflammation of the arm, whereof

3 proved fatal.

Vaccination, in the greater number of counties from which reports have been received, appears to be increasing: in the metropolis it is on the decrease.

The principal reasons assigned for the decrease are—

Imperfect vaccination,
Instances of small-pox after vaccination,
Supposed bad consequences,
Publications against the practice,
Popular prejudices.

Dr. GREENE, BOSTON, U.S., 1806,

Reported to the Boston Society of Medical Improvement a fatal case of erysipelas following re-vaccination.

* Dr. JENNER,

Writing to James Moore, in 1810, said, "When I found Dr. Woodville about to publish his pamphlet relative to the eruptive cases at the Small-pox Hospital, I intreated him in the strongest terms, both by letter and conversation, not to do a thing that would so much disturb the progress of vaccination."—*Life of Jenner*, ii., 374.

* Dr. CAPADOSE, The Hague, Holland, 1823.

We may expect a similar effect of vaccination as if we tried to protect the body against those terrible ulcers by inoculating their virus; and if inoculation of small-pox be dangerous, vaccination must be so too. The deleterious virus in the lymph being a poisonous germ, the application of it will be tantamount to poisoning the blood, whether the lymph be taken from cows or from children. As every remedy ought to be applied according to the particular constitution, the state of health, and the disposition of the patient, the uniform and universal use of the same means or virus promiscuously to every person, whether infant, adult, or aged person, will cause the prophylactic remedy, like all *specifics*, to be condemned as quackery. No one can tell what will be the effect of the nostrum upon the health of every one to whom it is administered. Science is plunged into an ocean of uncertainty, and the more you re-vaccinate the more you will complicate your course; and as it ought to be left to every one to take care of his own health and that of his children, or to take the advice of the physician in whom he has confidence, and to follow the way his constitution requires, compulsory vaccination ought not to be entertained.—*Bestryding der Vaccine.* 2nd Edition.

GEORGE GREGORY, M.D., 1840.

I have heard the particulars of a case where erysipelas and cow-pox co-existed, and the lymph being unfortunately taken, both diseases were communicated to the child. I have no experience bearing on the question whether measles can be communicated along with cow-pox, but it would be going too far to say that such a thing is impossible. As little have I to say practically on the question of communicating syphilis by means of the vaccine virus, but I am not prepared to deny the possibility of such an occurrence. DR. JENNER, as we all know, laid great stress on the danger of vaccinating while the system was pre-occupied by herpes, lepra, or psoriasis. I have frequently seen the vaccine vesicle assume the leprous character; nor can I doubt that the combination of the leprous and true vaccine disease would be propagated, if anyone were so unwise as to employ such degenerated lymph.—*London Medical Gazette.* P. 658. Vol. xxvi.

DR. HENRY COLES, Cheltenham, 1840.

A medical friend in this place, (much my senior, and whose authority, consequently, is much weightier than mine,) lately pronounced on an eruptive case, that it arose from the child having been vaccinated from an unhealthy subject. I have been astonished at the number of persons from whom I have heard of this child "turned into a most horrid spectacle;" and I find that the caution of parents (always in the extreme on this point), has of late been aggravated to a very annoying extent. It is not enough to be able to answer for the parents of the child, but I have had enquiries put to me respecting the preceding generation, and if the fancies and fears of the idle and wealthy are to be sanctioned and encouraged, it will be soon expedient that practitioners in this place should furnish themselves with the genealogy of all the clodpoles in Gloucestershire, together with a record of the integrity of their constitutions, and a voucher for the purity of their morals.—*London Medical Gazette.* P. 626. Vol. xxvi.

THE LANCET, March 30th, 1840.

It appears that there still exists in Italy, not only among the people, but many medical men, a great prejudice against vaccination; diseases which occur after vaccination being often attributed to the inoculation of the virus.

DUBLIN JOURNAL OF MEDICAL SCIENCE, 1844,

Publishes a series of cases of erysipelas following vaccination.

✿ Professor JOSEPH JONES, M.D.

It is said that in 1849-50 Erysipelas so frequently followed vaccination in Boston, and the result was so often fatal, that many physicians refused to vaccinate, except when it was absolutely necessary, and almost entirely abandoned re-vaccination.—*Researches upon Spurious Vaccination, Nashville, Tennessee, U.S.*

✿ Professor BARTLETT, of New York, 1850.

Lecturing at the University of New York, in 1850, on the causes of pulmonary consumption, quoted on the authority of two eminent French physicians, Dr. Barthez and Dr. Rilliez, the following important facts connected with vaccination: "Of 208 children that had been *vaccinated*, 138 died of tubercular consumption, and 70 of other maladies. In 95 who were *not* vaccinated, only 30 died of tubercular consumption, and 65 of other diseases." The circumstances, adds Dr. Bartlett, "connected with the two classes, the vaccinated and un-vaccinated, were, as nearly as could be, the same."

✿ Dr. VERDE de LISLE, 1850.

How is it that in an enlightened century, the Academy of Medicine, which is the centre and stimulus of this great question, tries to support a pitiable prejudice, not by solid and irrefutable reasons, but by pomposity, prizes, medals, and admonitions? It is high time, in the interest of science and humanity, to stop, and show how this vile, beastly corruption of the blood has injured our race. It is high time for the Academy to take up again this question among its labours, if it would not burden itself with a heavy responsibility for all the misery with which vaccination has already afflicted from three to four generations. It is time to examine whether Jenner and his coadjutors, in order to have their so called protective remedy against small-pox adopted, had the dishonest view to deceive the Government and public about the real nature of their specific.

In case of an affirmative answer, we will ask the Academy:—

1. Whether by the transplantation of a skin disease from an animal to the human creature, other affections beside a skin disease are not transferred?

2. Whether, in consequence of the transfer of these skin diseases, the absorbing and resorbing ability of the skin vessels is not also partly destroyed?

3. Whether, in consequence of this effect, the loathsome eruptive matters destined by nature to be thrown out of our economy, do not find an insurmountable barrier in the skin, and are therefore com-

pelled to develop themselves in the interior in various forms ; and whether these vaccinal disorganisations are not infinitely more serious, and a hundred times more fatal, than the natural small-pox, which the vaccine poisoning offers to prevent ?

4. Whether the number of these diseases, which have so luxuriantly grown since the introduction of the cow-pox, are not the effects of vaccination ?

✿ Dr. NITTINGER, of STUTTGART, 1850.

How rapidly does the scourge progress ! The terrible, ominous commotion begins already the first, fourth, seventh, and ninth day after the vaccination ; many, many children fall its victims ; and again others are more fortunate, but mostly some misery remains.

The mucous membranes, particularly those of the organs of the senses and generation, (in adults.) attest the sufferings and dangers originating in the inoculated kine pox poison—ophthalmia, otorrhœa, fluor albus, prurigo, &c.—*Evils of Vaccination.*

✿ Dr. COPELAND, 1850.

Just half a century has elapsed since the discovery and introduction of vaccination, and after a quarter of a century of the most transcendant laudation of the measure, and after another quarter of a century of reverberated encomiums from well-paid Vaccination Boards, raised with a view of overbearing the increased murmurings of disbelief (now rapidly increasing) among those who observe and think for themselves ; the middle of the nineteenth century finds the majority of the profession in all latitudes and hemispheres, doubtful as to the preponderance of advantages present and prospective, to be obtained either from inoculation or vaccination. Dr. Copeland also says,—that vaccination favours the prevalence of several forms of scrofula..—*Dictionary of Practical Medicine.* P. 823.

✿ The MEDICAL TIMES & GAZETTE for Jan. 1st, 1854,

Also informs us that consumption "has widely spread since the introduction of vaccination, and within ten years (ending 1853) had slain its 68,204 victims in the metropolis alone."

THE LANCET, July 15th, 1854.

There is a belief, it may be denounced as a prejudice, but it is not the less a deeply rooted conviction, and one not confined to the

poor or the ignorant, that, if the vaccine disease may be transmitted by inoculation, other diseases, less beneficial, may be propagated in the same manner, and by the same operation. Many a parent of high and low degree, dates constitutional disease in her offspring to vaccination with bad matter. Who should say that this etiological conclusion is always false ?

THE LANCET, Nov. 11th, 1854.

So widely extended is the dread that along with the prophylactic remedy something else may be inoculated—lest the germ of future disease may be planted, that few medical practitioners would care to vaccinate their own children from a source of the purity of which they were not well assured.

Dr. R. T. TRALL, New York, 1855.

Physicians are not at all agreed as to the propriety of resorting to vaccination as a protection from small-pox. There is no question that it is, to a great extent, a protection from the virulence and danger of the natural small-pox ; at the same time, there is danger of inoculating the patient with some loathsome, and even worse disease, as syphilis or scrofula, from the impossibility of always getting a supply of matter from healthy constitutions. In either way there is a risk to incur, and it is a delicate matter for a physician to advise on a subject when both sides are hazardous. I am fully convinced, that if people could bring up their children in strict physiological habits, the non-vaccinating plan would be altogether the best ; but in a city this seems next to impossible, and in the country it is pretty generally neglected. Children reared healthily in relation to food, exercise, and ventilation, have little to fear from any disease, however contagious ; they may have this (small-pox), but it will not endanger life, nor produce much deformity, nor serious injury. I have seen within the last year a most horridly loathsome case of scrofulous disease, in which the patient literally rotted alive at the age of 15, from unhealthy virus received when he was but three years of age. Parents often find some of their children tainted with morbid humours, unlike any other member of the family, and which they are wholly unable to account for, except on the supposition of foul matter taken into the system by vaccination. My own practice would be to keep children as healthy as possible ; and if the small-pox happen, let it have its natural course.—*Hydropathic Encyclopædia.* P. 96 & 97.

Dr. T. S. McALL, of Greenock.

I have every reason to believe that lymph taken from a party with hereditary disease, conveys that disease with it.—*Reply to Circular of Medical Officer of Privy Council, as to Vaccination*, 1856.

Dr. HAMERNIK, Prague.

The operation of vaccination is not in itself so insignificant as has been supposed, and very frequently is followed by results more or less injurious. At one period it was declared that from 1 to 2 per cent. of vaccinated cases ended fatally. Cases have frequently been observed in which vaccination has been followed by St. Vitus' dance, swelling of the glands of the shoulder and arm, abscesses, withering up of the punctured and the surrounding parts, accompanied by shivering attacks ; increased heat of the body, heightened pulse, &c. The deaths that have ensued from vaccination seem to have been caused by pyæmia, so-called, following upon it.—*Reply to Circular, Medical Officer of Privy Council*, 1856.

Dr. LEVER, Physician to Guy's Hospital, London.

I have known syphilis communicated to a child by the hand of a legally educated medical practitioner.—*Reply to Circular of Medical Officer of Privy Council.* 1856.

Dr. JOEL SHEW, Cincinnati, U.S.

Commenting on a case of death from vaccination which was reported in the "New York Journal, Medical and Surgical," gives a case of a lady whose health had been injured by vaccination, and adds,—

In two other cases large swellings took place ; one in the arm-pit, the other in the neck, lasting for some days, and finally breaking out in running sores. By questioning closely, we not unfrequently find that children never enjoy good health after vaccination, however firm it might have been before.

In another place the same author says,—

After all the recommendation that this practice has had for the last 50 years, there are yet those who entertain honest doubts as to whether it is, after all, on the whole, a benefit to the race. At any rate, the question, like all others, has two sides ; both of which demand our most honest consideration. It is certainly true that vaccination does not merit the encomiums which its more early advocates put upon it ; nor is it anything like capable of exterminating small-pox from the world, as was formerly maintained ; but

that it will, in a large proportion of cases, protect the system from variola, and that in those cases where it fails of this protection it renders the disease a much milder one, no one will pretend to deny. The only question is whether, as a whole, it is of benefit to mankind. It is maintained that vaccination, while it affords a good degree of protection from variola, yet renders the system more liable to other diseases. It is affirmed also, that other diseases are introduced into the system at the same time with the cow-pox. Long-continued and troublesome skin diseases appear to follow it, and in not a few cases the child seems never to enjoy good health after it has been performed. I think any one who has any considerable practice among children in any great city, will be struck with the number of cases he will find of this kind, by questioning parents on the subject. . . . . Not only does vaccination cause subsequent unfavourable effects, but it sometimes endangers life at the time; and in some instances destroys the child. I have myself known most fearful convulsions to be brought on by it, and that in children apparently of the firmest health.

Again he says,—

I have been for years so much a disbeliever in vaccination, that I would not be willing to have it practised upon a child of my own. —*Letter to President, Board of Health, by* JOHN GIBBS, ESQ. *Ordered to be printed by the House of Commons*, March 31st, 1856.

DR. W. F. LAURIE, L.R.C.P., L.S.A., Dunstable.

I vaccinated a child with pure lymph (reputed to be) from the Royal Vaccine Institution. The child, though previously apparently healthy, has ever since been nearly blind; opacities of the cornea developing themselves immediately after the operation. This case, and several others from other vaccinators, at Edlesborough, where it was performed, have militated very much against the practice of vaccination amongst the poor.—*Letter to* MR. JOHN GIBBS, *quoted in a Parliamentary Return, dated* 31st March, 1856.

D. JOSEF HERMANN, Chief of the Imperial Wiede Hospital, Vienna, from 1858 to 1864.

When a man has treated hundreds of cases of small-pox, both under sporadic and epidemic conditions, through many years and at all seasons, he comes to the decided conclusion that vaccination has not the remotest effect on the outbreak, course, or issue of the disease. Vaccinated persons, bearing unmistakeable marks of the process on their arms, frequently have confluent small-pox; while, at the same time, unvaccinated people have it in the mildest form. These observations, resting upon the most indubitable truth, appear

to have given occasion to the distinction between a *genuine* and a *modified* small-pox (varicella)—a distinction evidently made with the view of maintaining at all hazards the dogma to which vaccinators have committed themselves, as to the influence of vaccination in modifying the outbreaks of the epidemic. These clinical subtleties, belonging to the category of chimeras, have long since proved to be illusory ; in reality, there is *no such distinction* ; for, even in a mild epidemic of varicella, a careful observer will be able to discover amongst the sufferers fully developed pustules of small-pox, possessing every attribute of the true and genuine pustule.—*From the Naturarzt.*

*Dr. JOHN EPPS, 25 years Director of the Jennerian Institute, had vaccinated about 120,000 people, but finally declared, 1861—

The vaccine virus is a poison. As such it penetrates all organic systems, and infects them in such a way as to act repressively on the pox. It is neither antidote nor corrigent, nor does it neutralise the small-pox, but only paralyses the expansive power of a good constitution, so that the disease has to fall back upon the mucous membrane. Nobody has the right to transplant such a mischievous poison compulsorily into the life of a child. If the vaccine virus be not eliminated in the form of a genuine vaccine vesicle, the system is unquestionably poisoned. And again :—If the vaccine lymph does not produce the vaccine disease, it produces something else—*i.e.*, a noxious agent is introduced to poison the system against the poison of small-pox ; but if it does not produce this effect, it still poisons, without the benefit superadded of protection from small-pox.—*London Vaccine Institute Report*, 1863.

Professor RICORD, M.D., Paris.

If the transmission of disease is clearly demonstrated, vaccination must be altogether discontinued. For in the present state of science, we are in possession of *no criterion* that may permit the conscientious practitioner to assert that the lymph with which he inoculates is perfectly free from admixture with tainted blood. —*Lecture at the Hotel Dieu, Paris*, 1862.

At first I repelled the idea that syphilis could be transmitted by vaccination. The recurrence of facts appearing more and more confirmatory, I accepted the possibility, but still with reserve and even with repugnance ; but to-day *I hesitate no longer to proclaim their reality!—Address at the Academy of Medicine, Paris*, May 19th, 1863.

Professor RICORD, M.D., Paris.

My position is simply this—I suspect that isolated examples of syphilitic infection through vaccination are much more common in this country than is generally admitted. For the chance of the occurrence of such isolated cases is infinitely greater than that of a wholesale outbreak of vaccinal syphilis, and when such wholesale outbreaks have been noted, I cannot help feeling certain that many isolated cases of infection have occurred without their nature being detected or admitted.—*Letter to* Mr. W. Hume-Rothery, December 24th, 1879.

*MEDICAL TIMES & GAZETTE of May 30th, 1863.

On the 14th May, 1863, Mr. Wells vaccinated a lady, the mother of a family, taking good matter from the vesicle of a healthy child; immediately upon making the punctures the patient swooned. A visit on the following morning disclosed the fact of very singular symptoms having set in; the arm was much swollen, and had a dark purplish hue, much resembling the colour of a bullock's liver, the punctures nearly invisible, and the whole region of the operation presenting the appearance of having been bitten by some venomous reptile. The symptoms grew rapidly worse, entirely baffling medical skill, and the patient died on the 18th, of phlegmonous erysipelas.

Dr. O. KRATZ, Surgeon, Confederate Army, U.S.A.

After reporting cases of vaccine syphilis, says, "I have seen one case, where the product of vaccination was *Surpetigo rodens*, a frightful disease of, I believe, a cancerous character. Some cases had herpes exedens, as the result of vaccination on their arms.—*Confederate States Medical and Surgical Journal, pp.* 104, Vol. 1. 1864.

Dr. COLLINS, M.D., Licentiate of the Royal College of Physicians, Edinburgh, M.R.C.S., Eng., &c., 1866.

I have no faith in vaccination; nay, I look upon it with the greatest possible disgust, and firmly believe that it is often the medium of conveying many filthy and loathsome diseases from one child to another, and no protection whatever against small pox. Indeed, I consider we are now living in the Jennerian epoch for the slaughter of innocents, and the unthinking portion of the adult population.—(*Twenty years experience of a Public Vaccinator.*)

*Dr. FRANK HASTINGS HAMILTON, late Lieutenant Colonel, Medical Inspector, United States Army.

Vaccination almost constantly produces the same results (*i.e.*, ugly and untractable sores), and is in many cases followed by abscesses in the axillary, cervical, and other glands.—*Treatise on Military Surgery, quoted by* PROFESSOR JONES, *in Researches upon Spurious Vaccination.* P. 26. 1867.

*JOSEPH JONES, M.D., Professor of Physiology and Pathology, University, Nashville, U.S. 1868.

The Federal prisoners confined in Camp Sumpter, Andersonville, Georgia, were vaccinated, and in a number of cases large gangrenous ulcers appeared at the points where the vaccine lymph had been inserted, causing extensive destruction of tissues, exposing arteries, nerves and bones, and necessitating amputation in more than one instance. From the establishment of the prison, on Feb. 24, 1864, to Oct. 1, over 10,000 Federal prisoners died—*i.e.*, near one-third of the entire nnmber perished in less than seven months. These accidents led to the belief among some of the prisoners that the surgeons had intentionally introduced poisonous matter into their arms during vaccination. No wonder they had such a persuasion, seeing that about 100 of them lost the use of their arms, and about 200 were so injured that they soon afterwards died. Though some medical officers were tried before a special military commission, convened in accordance with orders from the War-office at Washington, on the charge of having wilfully poisoned the Federal prisoners with vaccine lymph, it was shown that the unhappy consequences of vaccination at Andersonville were paralleled in the Northern prisons. "After careful inquiries," says DR. JONES, "among returned Confederate prisoners, I am convinced that the accidents attending vaccination were quite as numerous and severe in Northern prisons as in Southern."—*Researches upon "Spurious Vaccination;" or, the Abnormal Phenomena accompanying and following Vaccination in the Confederate Army during the recent American Civil War*, 1861-65. *By* JOSEPH JONES, M.D., *Professor of Physiology and Pathology in the Medical Department of the University of Nashville, Tenn. (U.S.)*

T. MASSEY HARDING, M.R.C.S., L.S.A., House Surgeon to Middlesex Hospital; Public Vaccinator for 12 years in Worcestershire.

When a child is vaccinated about that time (dentition), and some eruption succeeds, it is difficult to say whether the vaccination or the dentition is the cause. It is not right, however, to view this

popular prejudice as a silly, groundless feeling, deserving only of ridicule. Deep-rooted popular opinions have generally a substratum of truth, and certainly some eruptive diseases have come on so immediately after vaccination as to render it extremely probable that the operation was the real cause of the eruption. These eruptions are generally of an eczematous nature—the skin is red, a serous fluid exudes freely. Most writers consider dentition the starting-point, and regard its occurrence after vaccination as a coincidence. This may be so, but the explanation certainly does not satisfy the parents of children in whom the eruption takes place immediately after vaccination, and would not satisfy me if it occurred in my own child in a few days after the punctures were made, and at the same time as the vesicle commenced. I bear in mind at this moment that a gentleman, aged fifty-six, not subject to any eruption, was re-vaccinated. The arm was violently inflamed, the matter, as he expressed it, took well. I have previously explained how mistaken such an expression is. This gentleman now, some two or three years after vaccination, is a martyr to an eczematous eruption over the body, and is himself much inclined to blame the vaccination. Some gentlemen, on the other hand, are such enthusiasts as to think that vaccination is capable of curing skin diseases of every variety, and gravely propose to employ it as a curative agent in skin diseases, including the syphilitic eruptions. —From *Small-pox and Vaccination*, published by the *Ladies' Sanitary Association*, London, 1868.

Dr. BALLARD, now one of Her Majesty's Vaccine Inspectors,

Summed up the evidence as follows:—

1.—There are numerous cases on record to prove that the vaccine virus and the syphilitic virus may be introduced at the same spot by the same puncture of the vaccinating lancet.

2.—From several instances on record, there can remain no reasonable doubt that the vaccine virus and the syphilitic virus may both be drawn at the same time, upon the same instrument, from one and the same vesicle.

3.—The vesicle which is thus capable of furnishing both vaccine and syphilitic virus may present, prior to being opened, all the normal and fully developed characters of a true Jennerian vesicle, as ordinarily met with.—*Essay on Vaccination.* Published 1868.

Dr. B. F. CORNELL, M.D., President of the Homœopathic Medical Society, of New York.

It is my firm conviction that Vaccination has been a curse instead of a blessing to the race; every physician knows that cutaneous

diseases have increased in frequency, severity, and variety, to an alarming extent. Not only the ancient forms of eruptive disease, scrofula, psora, erysipelas, tetter, &c., but new varieties are making their appearance, for which no satisfactory cause can be given, unless they are a compound of all the others, with a sprinkling of venereal to give them respectability; and, as contemporaries, a corresponding increase of chronic disease of all the internal organs. To what is this increase owing? contagion may account for some of the varieties; in a large majority, however, to no medium of transmission is the wide-spread dissemination of this class of disease so largely indebted as to Vaccination.—*Address delivered before the Homœopathic Medical Society of New York*, Feb. 11th, 1868.

*Dr. McCONNELL REED, M.D., L.R.C.P. Edin., 1869.

While some members of the medical profession declare it to be the result of their experience and general observation, that the practice of vaccination has increased the susceptibility to pulmonary consumption in adults, and the general mortality of infants and children —can you be surprised at the fact that there is a growing disinclination on the part of conscientious parents to submit to have their children vaccinated by compulsion? I confess that with my own experience as a medical practitioner, and with the knowledge of the experience and opinions of others capable of forming a correct judgment on this subject, I cannot advise my patients to have their children vaccinated: but I would strongly advise the Government to adopt measures to bring about a speedy repeal of the compulsory clauses of the vaccination acts.—Anglesea Place, Commercial Road, London, E.

Dr. SPENCER T. HALL, M.A.

He said his attention had long been drawn to this question, and the more he had looked into it, the more he had found evidence abounding in various parts of the kingdom—and this in every rank of life—of instances of persons being more unhealthy after vaccination than they were before. People of rank did not like to confess to the world that their blood was contaminated, though many of them had to mourn the fact in private life. Almost without exception—and he said this without unkindly feeling towards his medical brethren—it would be found that if a person well off wanted a child vaccinated, the doctor would seldom go to the parish

pauper for his lymph; but while this was going on, the poor pauper children were being vaccinated from one another by hundreds. Let us look this question fairly in the face.—*Southport Visitor*, Aug. 24th, 1869.

Mr. J. D. BROWN, F.R.C.S.E., L.S.A., of Haverford-west.

I have been 30 years in the profession, and have never vaccinated a child without trembling for the results; never sent to London for vaccine without a qualm of conscience, supplied (as it is well known to be) from the lowest grade of infected children, born of parents steeped in the most loathsome diseases, highly communicative by blood, lymph, and matter, and from that den of collected human ruin our pure lymph (save the mark!) is obtained.

This discovery that immortalised Jenner rescued the human race from the cruel tyranny and the hideous stamp of small-pox. Since that day the pure stream has passed through millions of human beings, taking some evil out of each—certainly all that can pass from blood to lymph, and therefore all that can be conveyed from man to man. What a tide of corruption it is by this time, I leave your readers to imagine, and how far it has lost its pristine power: how much polluted it must be with many nameless diseases, had better remain untold. Can we blame a mother, or punish a father, for refusing to convey this poison into their offspring's blood—a poison perhaps reeking with the stamp of a curse that never dies out till the awful sentence is fulfilled, and the fourth generation has suffered, in whose tomb it lies buried?—*Milford Haven Telegraph*, Sept. 22nd, 1869.

Dr. CHARLES KIDD

It is satisfactory to find that the poor woman imprisoned for neglect of vaccination has been set at liberty. Hudibras tells us of certain Puritans who are ever so exacting, perverse, and in the right, that they seem to worship God for spite. So it is to be feared of the animal vaccinators from the heifer, gushing sensationalists, and others who would wish to keep this woman in gaol, to point the moral of their new fangles. It is clear that we want some relaxation of these penal clauses as to vaccination. We want vaccination to be left in its natural channel, amongst proper medical men—not enforced by handcuffs and gaols, and the tender mercies of the police and mechanical-minded public vaccinators. I have seen a terrible disease in an infant that I could not, after the utmost inquiry, find

out to be due to anything but this compulsory vaccination of children in shoals, without discrimination. Such a thing could not happen in France or Ireland, where dispensary men are careful, conscientious, and well-educated; men who vaccinate half-a-dozen infants, perhaps, in a week,—not a hundred higgledy-piggledy by Act of Parliament. The mere crowding together of the children is a source of disease in itself. We have inspectors, who inspect after the harm is done; but what we want is less inspecting, and better preparation of the children for the operation, and an accurate and good vaccine lymph.—CHARLES KIDD, M.D., Sackville Street. *Anti-Vaccinator*, Oct. 2nd, 1869.

* DR. M. G. EVANS, M.D., Public Vaccinator for 16 years. Narberth, 1869.

Animal vaccination has been extensively tried on the Continent, and may have many good points about it; but competent judges affirm that the lymph obtained direct from the heifer acts too violently; and where could parties be found willing to supply heifers to keep up a stock of lymph? It is well known that in this country much more attention in general is devoted to the health of those animals, than is bestowed upon the health of the children of their proprietors, and who would not, for a small consideration, permit their stock to be operated on. Again; would it be justifiable to introduce into the system of animals a virus said to reek with the stamp of a curse, which animals (at some future date) are inevitably destined to become the food of man? Assuredly not. The idea is as loathsome as it is impracticable.—*Anti-Vaccinator*, October 23rd, 1869.

* DR. STOWELL.

[Twenty-five years a vaccine practitioner.] The nearly general declaration of my patients enables me to proclaim that vaccination is not only an illusion, but a curse for humanity. More than ridiculous—it is irrational to say that any corrupt matter taken from boils and blisters of an organic creature, could affect the human body otherwise than to injure it. First, it was asserted that vaccination protected for life. When this proved a failure, re-vaccination in every seventh year was proposed; but this also failed. Then there was a want of sufficient cow-pox. Well, cows were inoculated with human pox, and the suppurated matter produced by this operation was called pox-lymph, fresh from the cow. This bastard poison is

now transferred into human bodies, no matter what disease man or brute may have had; but it is called now-a-days "genuine vaccine." This *pure* lymph is carried from child to child, and spreads a diseased condition, so that hospitals and drug shops have increased 80 per cent., and continue to do so from day to day. What are 450 physicians of the Bluebook, while there are in London alone 3,000 physicians? I myself know the names of a hundred physicians who think like me.—*Lancet*, 1870.

* Dr. BAYARD.

For my part when I used to vaccinate, I observed many cases of ulcers sufficiently dangerous to necessitate particular care; and mothers, also, have said to me "My child has never been well since it was vaccinated." Consumption seized upon them and many succumbed. With this cow (or horse) virus I had introduced a germ of disintegration, and my preservative did not preserve them from small-pox.—*Essay on Vaccination, after* 35 *years experience.* London, 1870. *Translated by* George S. Gibbs, *Darlington.*

Mr. JOHN PRATT, M.R.C.S., Durham, 1870.

Was recently summoned, and he said to the magistrates: My child has not been vaccinated. I have reasons for not obeying the vaccination laws. I obeyed the law with respect to my first child, and the consequence is, that it has been seriously injured by the operation. Being a professional man, I used all the precaution I could in selecting good matter; but in spite of all that, my child has been considerably injured. Under these circumstances, I came to the determination that I would never vaccinate another child of my own or anybody's. I have considered the vaccination question for a number of years, and have gone minutely into it, both for and against; and the only conclusion I can arrive at is—that vaccination has no beneficial effect whatever, but that it inflicts very serious injuries. This being my opinion, I cannot conscientiously do an injury to any man's child, which I would do if I obeyed the vaccination laws.—*Co-operator*, July 30th, 1870.

* Mr. R. CEELY, M.R.C.S., L.S.A., of Aylesbury.

Dr. Seaton says (*Hand-book of Vaccination.* P. 337):—There is no one in England whose opinion on the subject of animal vaccination will be received with so much respect as Mr. Ceely's,

because there is no one who has nearly the knowledge that he possesses of the disease in the cow, and its transmission to the human species. He looks upon this proceeding as not only open to the objection of impractibility as applied to the general population, and of unsuccess; but he says also, that so far from being likely to produce fewer ailments, and cutaneous eruptions in the predisposed, he knows from his experience that it would, as being more irritating, produce more.

Dr. SKELTON, M.D., Licentiate in Medicine and Surgery, London, Edinburgh, and Glasgow; Author of the "Family Medical Adviser," "Science and Practice of Medicine," "Midwifery: its Complications, Diseases, &c., 1870."

The blood of the people is saturated with scrofulous and tuberculous diseases; and the prevailing opinion among thousands of the most thoughtful, non-professional and professional, is, that vaccination has much to do with it.

Dr. CHAPMAN,

In recording a case of eczema, resulting from vaccination, says: It may be here observed that chronic diseases may often be traced back to the period of vaccination in such a manner as to shew that the virus was communicated in that way.—*British Journal of Homœopathy.* No. 29.

Dr. TURNBULL, Cheltenham, 1870.

He was sure that there was not a single medical man who would not alter his views respecting vaccination, if he studied the subject for thirty-six hours. He had often stated that vaccination was physiologically wrong, and there was not a doctor living who could prove the reverse. He had seen healthy children die rotten, from the effects of vaccination; and although the doctors as a body, were opposed to him, yet he was glad to say that several medical men in Cheltenham had avowed their belief that several children in that town had been destroyed by vaccination.

ENOCH ROBINSON, M.R.C.S., late Medical Officer of Health for Dukinfield.

Before the child is three months old, it meets with another influence that is calculated to strengthen any infective process which may be already at work in the system, and originate such a process in a child otherwise healthy and vigorous. The most powerful infective substances are the various forms of purulent matter (a low condition of living animal matter, and essentially a phase of disease). One of these purulent forms of matter is the fluid of the vaccine vesicle. When inserted and absorbed into the living blood by an unnatural method, it exerts an influence of an infective character, opposed to the healthy vital power, and weakening to the extent of its influence the natural vigour of the body. That the natural vital powers are too strong for it in many cases, is recognised in the supposed necessity for re-vaccination. But in ascertaining the causes of the high rate of infant mortality, the degrading influence of vaccine matter must be considered.—*From Letter to the Local Board of Health on the Causes of High Infant Mortality in Dukinfield.*

Dr. HEIM, Public Vaccinator, Wurtemburg,

Says:—That the most expert diagnostician will not always be able to detect dyscrasy in children of the vaccination age, and that he himself has transplanted syphilis from a child which seemed to him perfectly healthy.—From *Horrors of Vaccination.* P. 26.

Dr. BAKEWELL, M.D., M.R.C.S., Vaccinator-General of Trinidad, 1871.

During the 21 years in which I have been in the habit of vaccinating, I have seen very few cases in which any skin disease followed the operation so soon after as to be fairly attributable to it. Nevertheless, I feel bound to say that the amount of testimony I have heard against it from mothers—and the number of cases of skin eruptions, especially, which they have declared to have followed vaccination in children previously free from anything of the kind—led me to infer either that some vaccinators have been very careless as to the sources of their lymph, or that certain constitutional diseases may be conveyed by vaccination.

Since I have been in Trinidad—and particularly since I have been Vaccinator-General—my attention has been much directed to the subject of leprosy, and its possible propagation by vaccination. It is a strange but undoubted fact, that leprosy is greatly increasing in this island; that it is attacking the children of most respectable parents, who want nothing in the way of diet, &c. And, moreover,

it is attacking the children of Europeans, where there can be no possibility of hereditary taint. Now, it is worthy of remark, that in this island vaccination has of late years been compulsory ; and that a large portion of the younger people were actually vaccinated during an epidemic of small-pox a few years ago. The general opinion among medical men is, that it is quite possible that leprosy may be propagated in this manner. It is curious, too, that in those islands where vaccination is not much used, there is very much less leprosy in proportion than here.

SIR WILLIAM GULL. Bart., M.D.

In the Commons Committee of 1871, was asked (Q. 4,869), "Have you known erysipelas to occur after re-vaccination ? Have you seen death resulting from it ?" Dr. Gull replied : "I have not *seen* death resulting from it, but I know that it has occurred."—*Minutes of Evidence.* P. 277.

PENNSYLVANIA MEDICAL JOURNAL, Sep. 1871.

American mothers at last are no more free from the plague of "vaccination" than are British parents. What a prospect for humanity is this propagation of loathsome, contagious diseases ! National virusation by a staff of State officers to "preserve" the public health. All the vaccine virus now sold in Alaska-street, Philadelphia, is obtained from children suffering under the influence of scrofula, syphilis, or some kindred pestilence. The vaccine station is neither more nor less than a cesspool of germinal horrors.

Dr. COLLINS, M.D., L.R.C.P. Ed., M.R.C.S.

There is no certainty in the action of the vaccine virus upon the constitution, it often imparts, or calls into activity, diseases that otherwise would have remained dormant, by debilitating the system and weakening the powers of vitality. 1871.

THOMAS SKINNER, M.D., L.R.C.S., Liverpool, 1872.

That there are many who die of vaccination I have no doubt whatever ; that they are maimed for life I have no doubt ; and that scrofulous and other forms of disease are rendered active by it every physician in family practice knows to be an almost every-day occurrence. I saw a case the other day where the little patient has never slept for three weeks, or very little, and it cannot be touched without screaming. It is much emaciated, and otherwise very ill. All this has arisen and dates from the day of its vaccination.

JOSEF HAMERNIK, M.D., Professor of the University of Prague, Bohemia.

Some years since, some terrible cases came to light, which were falsely registered as an epidemic, and which were caused by one vaccinator infecting a whole district with syphilis by vaccination.

In the begining of this year a similar misfortune occurred in the neighbourhood of Melnik, when a number of children in several districts got syphilis by vaccination, and several died of it.

Such epidemics probably occur more frequently than they are described as doing. In the earlier times of the practice of vaccination, no one dared to write anything against it, and thus no means existed of obtaining a correct knowledge of conditions like these.

One would naturally suppose that a single case of the transmission of syphilis by vaccination, incontestably proved, would result in the immediate abandonment of the practice of vaccination, in the instant withdrawal of the Government grant for its support, and in advising the people as to the dangers of vaccination, and showing the impossibility of any but misguided or self-interested physicians advocating its continuance.—*The History of Small-pox and Vaccination.* Prague, 1872.

Dr. J. EMERY CODERRE, Professor of Materia Medica, University, Montreal, Canada.

Vaccination has made victims among us; some have contracted small-pox in consequence of the inoculation of the vaccine; others have been attacked with gangrenous ulcers, syphilitic sores, &c., resulting from the introduction of this virus into the constitution.—*From a Paper read before the Medical Society, Montreal,* January 31st, 1872.

Mr. F. T. PORTER, M.R.C.S.

With reference to revaccination, I have no faith in it. Not one of the 36 attendants at the South Dublin Union sheds has taken small-pox. Only 7 of the number were revaccinated, and as the remaining 29 enjoyed the same immunity, wherein is the necessity of the operation? I have known gouty inflammation, abscess of the breast, (*angio-leucitis*), &c., to result from the operation. I cannot in the face of such facts approve of it. Moreover, the sense of the profession is against it.—*Medical Press and Circular,* March 27th, 1872.

Dr. STARTIN.

Believed in 30 years he had seen about thirty cases of syphilis communicated by vaccination. He had seen hundreds of cases of spurious vaccination, where contagious *porrigo* had been inoculated. He had seen *scabies* vaccinated on more than one occasion. When Dr. Simon sent out his circular, in 1856, he (Dr. Startin) collected several cases, giving the names and addresses of the patients, but no notice had been taken of them. They were undoubtedly cases where the children had been perfectly healthy, as well as their parents and nurses.—*Discussion at the Royal Medico-Chirurgical Society*, June, 1872.

WILLIAM HITCHMAN, M.D., D.C.L.

I have been acquainted with the morbid effects of vaccination for nearly 40 years, and have witnessed crowds of cases, both in hospitals and private practice, analogous to the Guy's Hospital model; but lest my testimony may not be deemed sufficiently impartial or unbiassed, I shall quote from the records of the Small-pox Hospital, to prove that pure lymph, even in the hands of Mr. Marson himself, is occasionally attended with very impure consequences. M. A. W., aged 4, a fine child, was vaccinated by Mr. Marson in five places on the left arm, the poor child at the time being in perfect health, on the 19th May. The arms soon became severely inflamed, and spots of purpura appeared on the face. The vesicles on the eighth day appeared dark and filled with blood, and numerous effusions were dispersed over the entire body. The areola assumed a mahogany appearance. In fact, the vaccine vesicles were jet black with fearful blotches—worse, I think, than the eruption of small-pox itself—dispersed (as I have said) over the whole body of this unhappy child thus "protected" by a paternal Government from disease; more especially involving the face, neck, and arms, and over the skin, together with bleeding from the left ear and nostril. Enough, and to spare, of these morbid phenomena now propagated by Acts of Parliament.—*The Anti-Vaccinator*, Oct. 7th, 1871.

As for the children recently vaccinated in Liverpool, I may say, from my own private observation, *without reference to the many thousands I have seen at the hospital for skin diseases*, that the health of hundreds has been thereby permanently affected with intractable forms of cutaneous eruption: emphatically have I seen strumous ulcers rapidly developed, acute ophthalmia, chronic enlargements of the cervical glands, diseases of the scalp, purulent discharges, fœtid abscesses, and gangrenous inflammation of parts, followed by sloughing, while the throat, especially, of many such miserable sufferers *according to Act of Parliament*, together with

the palate, uvula, and tonsils, are periodically covered with dark livid incrustations, more difficult to heal than those of small-pox itself, inasmuch as they owe their disgusting origin to the foul exudations of that indefinite, nameless, hideous thing now in course of active propagation throughout the land, yclept *vaccino-syphilis.* —From *The Anti-Vaccinator*, Dec. 16th, 1872.

Dr HENRY A. MARTIN, Boston, U.S.A.

The reason why, in February, 1873, I abruptly ceased to propagate and collect humanized virus was, because in one week of that month I had five cases of erysipelas. They were all in children vaccinated on one arm with the institution "stock" and on the other with cow-pox; and in every instance the disease appeared on the humanized side. I had previously had four precisely similar cases scattered over the preceding two and a half years, and contemplated an eventual abandonment of the old stock; but this epidemic determined me at once to discontinue vaccination with humanized virus.—*Unfortunate Results of Vaccination.*

MEDICAL TIMES & GAZETTE, February 1st, 1873.

The important subject of vaccinal syphilis came again before the Medico-Chirurgical Society on Tuesday evening, when a paper was read by Mr. HUTCHINSON, detailing two new cases. He also drew some general deductions from the facts as already ascertained, which, together with others elicited in the course of the discussion that followed, constitute the most important practical suggestions yet made with regard to this most unsatisfactory subject. That syphilis could be communicated by vaccination was, though admitted abroad, long disputed in this country. Since the publication of MR. HUTCHINSON'S paper, and a communication by MR. THOMAS SMITH to the Clinical Society, where the patient was exhibited, it can no longer be so. We have now emerged from the region of doubt, to one of belief in the possibility of such an untoward occurrence; and, in accordance with the practical turn which most professional discussions sooner or later take in this country, we have promptly begun to seek a remedy for the possible evil.

Heretofore, as we have said, it has not been admitted that, if due care be taken, syphilitic infection by vaccination is possible. Especially has this been urged by the Crown officers when asked to encourage heifer vaccination. The facts now before the public will tend to rouse them, if they have not been roused already, from the false security into which they have been lulled. And, as was stated at the meeting, it is plain that our compulsory vaccination laws cannot be maintained unmodified.

EDWIN HEARN, M.B., F.R.C.S., Southampton.

I have always contended that compulsory stational vaccination necessarily enforced the obtaining of lymph from uncertain sources, possibly more than ninety in a hundred vaccinated at stations being strangers, and their constitutions absolutely unknown. Hence the vaccine lymph, taken after the most superficial inspection —such as I have personally witnessed— must prove a fertile source of blood diseases, in support of which I can relate a striking instance within my own experience. A number of children were vaccinated with lymph supplied from a vaccination station. No cow-pox resulted ; but in every case a troublesome bullous eruption, which only yielded to specific treatment after many weeks. In no instance have I traced a like disaster where the lymph has been taken from home vaccinations, the constitution of the vaccinated being almost invariably known to the family medical attendant.—*The Anti-Vaccinator*, Feb. 3rd, 1873.

Prof. A. TROUSSEAU, M.D., late Physician to the Hotel Dieu, Paris.

The transmission of syphilis by vaccination appears now to be an established fact. To the examples, which, since the beginning of this century, have been reported, and of which the number is singularly augmented of late years, in France as well as abroad, I could add that which has come to our notice in our hospital.

A young woman of eighteen came to be treated for an affection of the uterus. As small-pox was present I advised her to be vaccinated. The vaccine was taken from a child *perfectly healthy in appearance*, and which also furnished vaccine for four other children. With the children a legitimate vaccination was produced, and, during the 5, 10, 15, and 20 days respectively they remained in the hospital, nothing unusual was observed, but unfortunately, we lost sight of them. With the young woman, the day after inoculation the puncture became swollen, surrounded by inflamed areola, and, with sharp irritation of the skin. Four or five days after *all traces had disappeared.* At this period she left the hospital—to return in 15 days to have the uterine complaint treated. On her return she remarked that since quitting the hospital the inoculations on her left arm had taken . . . . we recognised ecthymous pustules. On her second return, a fortnight later, her condition left no doubt of a serious syphilitic infection, of which the origin was incontestably in the vaccinal punctures.

If there are still some doctors who doubt the possibility of the transmission of syphilis by vaccination, the greater number have

succumbed to the evidence . . . . amongst these latter, some say it may be conveyed by the vaccine virus, whilst others consider it can only be done by blood being taken with the lymph . . . . Like M. VIENNOIS, I am of opinion it is important never to take vaccine from a child *before the age* at which hereditary syphilis usually manifests itself, that is, before the age of *four or five months;* for such syphilis, whether outwardly apparent or not, can be transmitted. . . . . The assertion that blood only conveys the disease is more hypothetical than demonstrated. It is difficult to understand that what the blood serum contains the vaccinal serum does not contain also; indeed, it is practically very difficult to take vaccine without any mixture of blood.—From the *Clinique Medicale.* Vol. I., pp. 116-8. Paris, 1874.

MR. HENRY MAY, M.R.C.S.,

Contributes an article on "Certificates of Death," from which we quote as follows, viz :—

In certificates given by us voluntarily, and to which the public have access, *it is scarcely to be expected that a medical man will give opinions which may tell against or reflect upon himself in any way*, or which are likely to cause annoyance or injury to the survivors. In such cases he will most likely tell the truth, *but not the whole truth, and assign some prominent symptom of the disease as the cause of death.*

As instances of cases which may tell against the medical man himself, I will mention *erysipelas from vaccination*, and puerperal fever. A death from the first cause occurred not long ago in my practice. and although I had not vaccinated the child, *yet in my desire to preserve vaccination from reproach, I omitted all mention of it from my certificate of death.—Birmingham Medical Review*, January 1874.

J. MACKENZIE, M.D., F.R.C.P., Edinburgh.

I was vaccinated in 1806, yet had the small-pox in 1820. Last year, I got details of a vaccination massacre at Appleby, from the mistress of the family servant (a groom), who let me enter names, dates, &c., in my memorandum book. I communicated the information to a friend, who, asking for more details, was told I must have imagined the story. Last week a note says they have, at last, excavated the truth, the mother praying for advice how to save her new baby from the fate of her other children. No wonder the Devil is called "the father of lies."—*Eleanach, Inverness*, Nov. 30th, 1874.

*Dr. BRAY.

Facts have accumulated to show that since vaccination had become the law of the land, consumption, which before was comparatively unknown in this country, had, as it were, become an inheritance in certain families. The pure lymph perhaps obtained from the greasy heels of a dismal old horse, was identical with the matter ejected from the lungs of a consumptive person. When a child was vaccinated it might happen no particularly observable disturbance took place. But there was an instrument used by medical men called a laryngoscope—a sort of reflecting spy-glass, by which the bronchial tubes could be examined. When the vaccinated child's respiratory organs were submitted to this introspection, the mucous membrane would almost invariably be found studded with innumerable atomic pustules—the first garnered fruits of the process, and the damning evidence of what might be expected to follow in its train. Vaccination was applied to the arm, but the poison diffused itself rapidly into the lungs, the blood, the stomach, and even the brain. A child, "whom nobody owned," was killed in the streets of Paris, and given over to the medical men for anatomical purposes. In the breathing tubes, thorax, and stomach, were found upwards of 15,000 distinct ulcerations. The matter was scooped out, and a living child vaccinated with it! It produced all the symptoms of the "true lymph." Like produced like. The matter of diseased lungs would produce in another subject, lung disease.—*Extract from Speech, Market Rasen, in C.V.L. Circular*, 1876.

Professor ROBERT A. GUNN, M.D., New York, 1877.

Even if there was any evidence to prove that vaccination was a prophylactic against small-pox, the appalling evils that have been and are still produced by it are sufficient to condemn the practice as a crime.

Every physician of experience has met with numerous cases of cutaneous eruptions, erysipelas, and syphilis, which were directly traceable to vaccination, and if these could all be collected and presented in one report, they would form a more terrible picture than the worst that has ever been drawn to portray the horrors of small-pox.—*Vaccination, its Fallacies and Evils*, P. 13.

BRITISH MEDICAL JOURNAL, 1877.

In addition to the fact that people are ill after vaccination, it is important to remember that people die after the operation, if not from the disease itself, at least from its sequelæ, notably erysipelas.

ROBERT LIVEING, M.D., F.R.C.P., A.M., Physician to the Skin Department, Middlesex Hospital.

Vaccination frequently produces an attack of eczema, simply by setting up local irritation.—*Treatment of Skin Diseases.* P. 7, 1877.

It often happens that vaccination is attended with more or less irritation or inflammation of the skin of the arm, in some cases to subacute eczema. P. 90.

CHARLES T. PEARCE, M.R.C.S.

Let me now direct your attention to the sad increase of infantile erysipelas concurrently with the increased number of infantile vaccinations.

Taking the five years 1860-4, and contrasting them with five more recent years 1870-4, we find the following figures :—

DEATHS FROM ERYSIPELAS.

Periods of 5 years.		Under 1 year old	Under 5 years old	All ages.
1st period	1860-1-2-3-4	2,698	3,280	8,754
2nd period	1870-1-2-3-4	3,550	4,021	11,600

Thus the lamentable fact is apparent, that of the deaths from Erysipelas at *all ages*, nearly one-third occurred in the *first year of life*—the year of vaccination—while the total number was greatly in excess of that which can be accounted for by increase of population.

Erysipelas is *now* an infantile disease, and it is to be noted that erysipelatous symptoms are the recognised effects of proper vaccination. The connection, therefore, between vaccination and erysipelas is established.

The annexed table shows the increase from one period of five years to the other of the three diseases referred to :—

Five years	Deaths from Small-pox	Deaths from Erysipelas			Deaths from Syphilis	
		Under 1 year	Under 5 years	All ages.	Under 1 year	All ages
1st period, 1860-1-2-3-4	19,346	2,698	3,280	8,754	4,504	6,425
2nd period, 1870-1-2-3-4	49,366	3,550	4,021	11,600	7,009	9,271

Beyond all this sad increase of suffering and mortality, there is another serious aspect of the question—the increasing resistance of the people to a law they consider oppressive, because they are unconvinced of the efficacy of the process it enforces, while of its accompanying dangers they have, as they believe, sufficient evidence. —*Letter to* RIGHT HON. G. SCLATER-BOOTH. M.P. Feb. 20th, 1877.

Mr. BRUDENELL CARTER, F.R.C.S., L.S.A., Ophthalmic Surgeon to St. George's Hospital.

I think that syphilitic contamination by vaccine lymph is by no means an unusual occurence, and that it is very generally overlooked because people do not know either when or where to look for it. I think that a large proportion of the cases of apparently inherited syphilis are in reality vaccinal; and that the syphilis in these cases does not show itself until the age of from eight to ten years, by which time the relation between cause and effect is apt to be lost sight of.—*Medical Examiner*, May 24th, 1877.

Mr. JONATHAN HUTCHINSON, F.R.C.S., Surgeon to the London Hospital, 1877.

There can be no doubt that the danger of transmitting syphilis by vaccination, is a real and a very important one.

Amongst the best means by which we may hope to prevent the occurrence of these lamentable accidents (referring to a series of cases of vaccinal syphilisation) in the future, I would put, as the foremost, the *diffusion of the knowledge amongst the profession* that such accidents are possible. Until my original papers were published almost the whole British profession was incredulous on this point; and in spite of the publicity which was then given to the facts there still remain, I believe, some who are either uninformed or unconvinced.—*Illustrations of Clinical Surgery—Vaccination Syphilis*, 1877.

C. SPINZIG, M.D., St. Louis.

Vaccination is tantamount to inoculation and constitutes *septic poisoning*—a criminal offence to human health and life—and is statistically proved to afford no protective or mitigating power over small-pox, and scientifically, in the nature of the case, it cannot possess any.—*Variola: its Causes, Nature, &c.*, 1878.

J. GARTH WILKINSON, M.R.C.S., Edin., 1878.

At first sight, especially to confirmed vaccinators, nothing seems wilder, or more wide of the mark, than the assertion, frequently made, that vaccination causes a large and ever-enlarging disease-rate and death-rate by maladies quite different from the vaccine disease. This is particularly the case, because the effects of vaccination are scarcely ever kept in view by the practitioner for more than a few weeks from the operation. After such a date he honestly, but

ignorantly, scouts the suggestion from parents and non-professionals that such and such results are due to his deed, and that the child has never been the same since that deed was done. It is not to be expected of him that he shall consent to trace effects years afterwards, and throughout life, to the same trifling puncture which he inflicted, like Emile Ollivier's first prick of war, "with a light heart."

Hundreds of cases are recorded in which the deaths of infants who were healthy up to the hour of vaccination followed, after greater or lesser periods of suffering, often horrible suffering, the insertion of vaccine; the suffering generally dating from the operation, and disease steadily advancing therefrom. The vaccinating doctors for the most part deny all connection between the vaccination and the death, and influence coroners' juries to pronounce death from some other cause. The difficulty is that the circumstantial witnesses of the death are *only mothers, fathers, and relations*, and their testimony is of no weight in scientific scales. The very reason that they love makes them foolish in comparison to the impartial doctor—if only he were impartial.—*Vaccination Tracts.* No. 13.

Dr. HOEBER, Hamburg.

Vaccination is extremely prone to develop disease, being an attack upon the system in early childhood, when *owing to teething, there is already a great predisposition towards disease.* Also vaccination involves a penetrant diseasing of the whole body. This lowers all the natural powers of resistance in the child, and as a consequence, illnesses of various kinds, scrofulous, bronchial, &c., frequently follow.—*Der Praktische Arzt*, January, 1878.

CONSTANTINE HERING, M.D., Philadelphia.

I have more than once plainly seen, and often heard of, cases where children remained ailing from the time of vaccination, who were previously in robust health. If this occurred with but one tenth the number of cases, or even less, it were sufficient to call up the wish for a better preventive.—*From Letter dedicated to the Homœopathic Practitioners of Great Britain, Philadelphia*, Aug., 1878.

*Professor GERMANN, M.D., of the University of Leipsic.

Above all, the dire fatality which lately occurred at Lebus, a suburb of Frankfort-on-the-Oder, would alone warrant the abolition of the vaccination laws. Eighteen school girls, averaging 12 years

of age, were re-vaccinated, and thereby syphilised, and some of them died. . . . Yet the lymph, the syphilitic lymph, used in this case was obtained from the Official Royal Establishment for the new "regenerated" or "animalized" vaccine lymph so warmly recommended for the re-vaccination of schools.—*Petition to German Diet*, 1878.

Dr. SAMUEL EADON, M.A., Gloucester, 1879

The lymph, obtained from the ulcers of children, by means of arm-to-arm vaccination, conveying, in addition to the hereditary taints of animals (as those of the rinderpest, cattle-plague, steppe-murrain, &c.), the sins of the fathers to the third and fourth generation, is imported into the young organism besides. Is there any wonder, with such abominable fouling of the human body, that consumption, scrofula, syphilis, cancer, and the whole vile train of skin diseases, should start up, and rage on with maddening intensity, making life miserable, swelling, to a dreadful extent, the bills of mortality, and curtailing, by many years, the length of human life?

Dr. NIEMEYER, of Tübingen, 1879.

It cannot be denied that vaccination sometimes endangers life, and in other cases leaves permanent impairment of health, especially cutaneous diseases and other *scrofulous* affections, due to the debilitating influence of the fever accompanying the vaccinia. —*Text Book of Medicine.* 1879.

ALEXANDER WILDER, M.D., Professor of Physiology, New York, 1879.

No man has the right to disease another on any pretext. If vaccination was prophylactic against small-pox, its infliction would nevertheless be wrong and without justification. It is not thus prophylactic, and therefore ought to be resisted. The medical man who vaccinates, or advocates vaccination, does it in the very face of science, and as an empiric solely. Vaccination tends directly to impair the integrity of the body. It is certainly the profaning of everything sacred in a person. When this impairment has occurred, the person will always be more liable than ever to sickness and epidemics. Hence a vaccinated people will always be a sickly people, shorter lived, and degenerate.

J. R. NEWTON, M.D., Boston, U.S.A., 1879.

Vaccination is a practice that causes a vast amount of disease and suffering. Its effects are far more terrible than the disease it is designed to prevent. No matter how pure the vaccine matter may appear to be, virus is left in the system, which will, sooner or later, be developed in scrofula or some other filthy disease. Were I to relate a few of the cases that have fallen under my observation of persons injured by this practice, it would fill the mind with horror.

W. BRUCE CLARKE, M.B., F.R.C.S.,

Records a case of "Pyæmia after vaccination—Death," in a child at 14 weeks. Nothing unusual was noticed until after the 8th day; an abscess formed in the left axilla, and others on right forearm, right thigh, and left wrist. The temperature rose to 103·4, and the child died exhausted on the 19th day after the vaccination. —*St. Bartholomew's Hospital Reports*, 1879. Vol. xv.

WILLIAM FORBES LAURIE, M.D., Edin., St. Saviour's Cancer Hospital, Regent's Park.

Being anxious not to do mischief to my fellow-creatures, and being, as regards my own family, liable to fine or imprisonment under the Compulsory Vaccination Act, I lately wrote to some M.P.'s on the subject. I asked them to come here and see for themselves the dismal results of vaccination in cases of paralysis, blindness of both eyes, hip-joint disease, consumption, and frightful forms of skin disease. Though I received replies they have not yet inspected the cases. I can add my testimony to that of Dr. Ange, who was 17 years engaged in the Isle of Wight in curing cancer, to the great increase of cancer all over the kingdom. This is attributed by some medical men to the large amount of syphilitic disease with which vaccine lymph is impregnated; by others to the direct impregnation of healthy persons with lymph imbued with scrofulous and cancerous matter. In this way they account for the large increase of cancer in all parts of the body, throughout the kingdom generally.—*Letter to* Mrs. Hume Rothery, June 3rd, 1879.

Dr. CHARLES CAMERON, M.P.

Referring to the precautions taken at the National Vaccine Establishment to secure purity of lymph, contended that they were at best based upon a very questionable theory, and were altogether inadequate to prevent the collection of lymph from infants in whom disease could only be detected on a close and minute examination,

such as those who had proved the source of so much mischief in MR. HUTCHINSON'S and some of M. DEPAUL'S cases. * * *

M. DEPAUL, the chief of the Vaccination Service of the French Academy of Medicine, became alive to the danger of the spread of syphilitic infection through vaccination. In a paper which M. DEPAUL published in 1867, which embraced the record of little over a year's French experience, there were enumerated half-a-dozen more or less extensive outbreaks of vaccinal syphilis, in the course of which upwards of 160 children had been infected, and several had lost their lives. It was not until 1871 that a case of wholesale syphilitic invaccination, brought before the Royal Medical and Surgical Society by MR. JONATHAN HUTCHINSON, incontestibly proved to the medical profession in this country that the theory on which they had so long relied was unsound.—*Address at the Calf Lymph Medical Conference*, Dec., 1879.

MR. JONATHAN HUTCHINSON, F.R.C S., &c.

At the ordinary meeting of the Royal Medico-Chirurgical Society, held on the 9th December, 1879, MR. HUTCHINSON described a case of Vaccinia Gangrenosa, and exhibited the body of the infant, who had been vaccinated three months before death, from the arm of a healthy child. Three other children vaccinated at the same time, from the same source, took no hurt. On the eighth day after vaccination, a papular and vesicular rash appeared over the trunk, which rapidly assumed a sloughing character. The eruption was at first taken for small-pox, and when death took place, a fortnight later, an inquest was held on the case, for it was then thought to be syphilis. But MR. HUTCHINSON pointed out that its evolution as well as its character were not those of syphilitic infection, and he considered it to be a true case of vaccinia passing on to a gangrenous condition—a condition he had sometimes observed to take place in varicella. The vaccine marks on the arm were natural.—*The Lancet*, December 13th, 1879, P. 873.

MR. SIMON, F.R.C.S.

When a given (animal) body is possessed by one of them, (contagious diseases) no product of that body can be warranted as safe *not* to convey the infection. Presumption against every part and product of the diseased body is by every one readily admitted, where there are vehement general symptoms of disease; but it is important to know that not only in such febrile states, but even in states of chronic dyscrasy, and even at times when the dyscrasy may be giving no outward sign, the infected body may be variously infective. Thus the vaccine lymph of the syphilitic may possibly

contain the syphilitic contagion in full vigour, even at moments when the patient who thus shows himself infective, has not on his own person any outward activity of syphilis. Similarly in regard to tubercular disease.—*British Medical Journal*, Dec. 13th, 1879.

✿ Dr. C. SPINZIG, St. Louis, U.S. 1880.

Jenner had already observed phlegmonous erysipelas to follow vaccination. And in the Foundling Hospital at Petersburg, of 5,000 vaccinated infants, 57 took erysipelas in consequence of vaccination and died. Also in Boston, erysipelas has been seen to follow upon vaccination; and on various occasions vaccination has had to be suspended.

Dr. A. G. SPRINGSTEEN, Cleveland, Ohio.

One pernicious practice, is that of *vaccinating* children. I am as afraid of the virus as I am of the small-pox. Not only scrofula, but other impurities have been conveyed to the blood of healthy persons by means of vaccination. No one, who has given the subject the least consideration, doubts that impurities may be conveyed in this manner.—*New York Medical Tribune*, January, 1880.

✿ Mr. J. H. BOYLE, M.B., C.M., L.M.,

Records a case of erysipelas, followed by large ulcerated, unhealthy sores in a previously healthy child, at six months, following vaccination with *calf lymph*.—*Lancet*, April 3rd, 1880.

Sir THOMAS WATSON, Bart., M.D., F.R.S., D.C.L.

There has fallen an ugly blot. It is too certain that one objection really formidable does exist—that the operation may, in some few instances, impart to the subject of it the poison of a hateful and destructive disease (syphilis), peculiar to the human species, and the fruit and Nemesis of its vices. On this distasteful subject I shall simply appeal to the printed testimony of Mr. Jonathan Hutchinson. . . . Such facts as he has *demonstrated*, constitute a rational excuse for objecting to compulsory vaccination *I can readily sympathise with, and even applaud a father* who, with the presumed dread or misgiving in his mind, is willing to submit to multiplied judicial penalties, *rather than expose his child to the risk of an affection so ghastly*.—*Nineteenth Century*, June, 1880.

Dr. EDWARD HAUGHTON.

I have now under treatment a girl who has an eruption, not unlike small-pox, on her shoulders, arms, and face, and which causes her intolerable itching. She was vaccinated 18 years ago, and has an eruption every summer of a similar kind to that which followed shortly after having been vaccinated. At these times she is greatly debilitated and looks thoroughly out of health. I have also just given up attending a gentleman who, having suffered from chronic eczema on the arms and legs, was recommended to try the experiment recorded in Dr. Joseph Kidd's book on *Therapeutics* (page 98), and get vaccinated with a view to cure. The result was a great increase of the disease, which almost drove him to despair. He is now nearly well. I have also seen an eruption, almost indistinguishable from small-pox, coming out on a patient round the site of the vaccine vesicle in a ring of several inches circumference. In this case no further harm resulted, but I am inclined to think that those cases which are said "not to take" are those in which the vital organs are most likely to be injuriously affected.—*Letter I. The British Medical Journal, Aug. 18th*, 1880.

T. L. NICHOLS, M.D., F.A.S.

Syphilis, scrofula, and probably every kind of blood poison can be taken by Vaccination, which, so far from being a protection against Small-pox, seems to have been one of the chief causes of the late epidemics. It is never safe to take matter from another body into our own: we risk taking all its diseases. There is no doubt thousands have been mortally poisoned by Vaccination.—*Esoteric Anthropology*. P. 186.

✡ WILLIAM HYCHEMAN, M.D., of New York, 1880,

Writing after 40 years practice as a physician, says:—Now vaccination by calf-pox, cow-pox, or humanized pox, whatever may be the multiplicity of lymphs, (and "pure vaccine" is only a rhetorical euphemism for horse-grease) is an eruptive disease, setting in with febrile symptoms, followed by papule, vesicle, and pustule, in about eight days. And what else is small-pox? I have recently dissected more than a dozen children, whose deaths were *caused* by vaccination, and no small-pox, however black, could have left more hideous traces of its malignant sores, foul sloughing, hearts empty or congested with clots, than did some of these examples of State physic, which killed with rotten patches of lungs, spleen, mesenteric glands, kidneys, and intestines. Shame! Indeed, scarcely a day elapses

but I am called upon to witness the sufferings of vaccinated children, in form of cerebral and gastric complications, persistent vomiting, bronchitis, diarrhœa, with pustules in the mouth and throat (pharynx), on the eyelids, and ulceration of the cornea, which remains opaque, and may lead to blindness.

Dr. BREWER, M.P.

In various classes, especially in large towns, not only was there doubt whether vaccination was effectual as a prevention, but there was an exceedingly great fear that diseases even more to be dreaded than small-pox itself were conveyed by vaccine matter.—*House of Commons.*

Professor BOCK, M.D., of Leipsic,

Said:—I have, in a forty years practice, seen far more evil than good from vaccination, and therefore vaccinated my own children only in their third and fourth years, when they were hearty and strong. *But I would never have vaccinated them but for an indirect compulsion.*

Mr. LANE, F.R.C.S.

It is clearly proved that syphilitic blood may convey syphilis, but it is not yet proved that vaccination lymph from a syphilitic child, even though unmixed with blood, will not do so, and it would, therefore be the height of imprudence to act on any such belief.—*Lane's Lectures on Syphilis*, 1881.

Dr. RICHARD NEALE, of 60, Boundary Road, St. John's Wood.

During the last few months, I have vaccinated between three and four hundred patients, and of these six or seven have gone off into dead faints, in one attended with vomiting, but in no instance followed by convulsions.—*British Medical Journal*, 25th June, 1881.

* Dr. DESJARDINS, Nice, 1881.

In a letter to the editor of the *Akhbar*, gives a complete confirmation of the syphilisation of the fifty-eight French soldiers in Algeria, on Dec. 30 last, the particulars of which we have already set before our readers. The most cautious silence, we are informed,

is preserved by the military authorities; and not without reason, if vaccination is to retain its hold on popular credulity. The writer demands that the recruits be dismissed from a service to which they will be a useless appendage, and proposes to solace them with pensions for injuries which the Government cannot redress. The letter concludes with a recommendation that calf-lymph be adopted in future. It is proclaimed, apparently by an inversion of the famous line, "A rose by any other name would smell as sweet," that numerous re-vaccinations have lately been made in the garrisons of Paris and Vincennes with "lymph from the calf."—*Journal d'Hygiene*, Aug. 25th, 1881.

MEDICAL TIMES & GAZETTE, September 3rd, 1881.

M. TOUSSAINT vaccinated a cow in an advanced stage of tuberculosis with lymph absolutely pure. The vesicles progressed normally, and with the lymph obtained from them he vaccinated different animals, all of whom subsequently became tuberculous. The significance of these experiments can scarcely be over-rated, for though a judicious vaccinator would not use lymph taken from a child who exhibited already evidence of the disease, the chances of cows in whom spontaneous vaccinia may appear, and whose lymph would at the present time be eagerly sought after, being, like so many of their species, tuberculous, would be great; and it would seem in consequence that *the dangers of animal vaccination may be greater than those of human*, which are supposed to be avoided by having recourse to the cow.

W. J. COLLINS, B.Sc., M.B., B.S., M.R.C.S.

In 1805 an anti-vaccinator, DR MOSELEY, discovered that syphilis was communicable by vaccination; it was not till 70 years later that the majority of the profession were convinced of the fact. It would be tedious to quote the list of eminent men who have averred their belief in this "ghastly risk," but it includes SIR THOMAS WATSON, PROFESSOR RICORD, DR. TROUSSEAU, MR. JONATHAN HUTCHINSON, MR. SIMON, DR BALLARD, MR. LANE, and a host of other distinguished syphilographers. DR. LANCEREAUX published a list of 258 authenticated cases of vaccino-syphilis, and more than 700 instances of the kind are now on record. MR. BRUDENELL CARTER believes that "a large proportion of cases of apparently inherited syphilis are in reality vaccinal," and this belief is shared by many. In 1877 MR. JONATHAN HUTCHINSON published full and detailed accounts of 24 persons who had been syphilised by vaccination, and he adds that "there can be no doubt that the danger of transmitting syphilis is a real and a very important one." Pathology

has taught us long since that syphilis may be conveyed by infected blood, or the secretions which are its offspring. Statistics complete the evidence by showing that the deaths from infantile syphilis per million births were, under enforced vaccination (1867-78), 1,738, as compared with 564 under voluntary vaccination (1847-53).

Next as to erysipelas. Many instances are on record in which erysipelas has supervened from one or two weeks after vaccination; perhaps the most notable of these is a little outbreak which occurred at Gainsborough in 1876, which was officially investigated by DR. NETTEN RADCLIFFE. Sixteen children were vaccinated with Government lymph by the public vaccinator; in 11 erysipelas followed, and six died of it. In 1877 MR. ERNEST HART, editor of the *British Medical Journal*, wrote, "It is important to remember that people die after vaccination, if not from the disease itself, at least from its sequelæ, notably erysipelas." DR. MARTIN writes of erysipelas, "that miserable complication, the pest of vaccinators." From 1865 to 1871, 96 deaths were recorded as due to "erysipelas after vaccination;" and it is probable more would be recorded were not silence on this subject counselled by medical officers of health in order "to preserve vaccination from reproach."

The occurrence of skin diseases after and from vaccination has been admitted, and cases in illustration have been published by HEBRA, LIVEING, HUTCHINSON, NIEMEYER, CEELY, and many others. Before the Vaccination Act, 183 infants out of every million died from skin diseases before they attained one year of age. Since the Act has been rigidly enforced the figure has risen steadily to 343.

One is told almost *ad nauseam* that the occurrence of erysipelas or skin disease after vaccination is purely accidental, is a matter of *post hoc*, not *propter hoc*, or that it was all the child's fault, or the result of the combination of some ill-understood meteorological conditions, in fact anything but vaccination. That was not JENNER'S opinion at all; he looked on accompanying erysipelas as the stamp of genuine cow-pox, and on one occasion obtained his lymph from "an extensive inflammation of an *erysipelatous* kind appearing without any apparent cause on the upper part of the thigh of a sucking colt!" I think under these circumstances we can hardly pretend to look upon vaccination as quite so innocent of erysipelas as the hypothetical scratch of a pin so often alluded to, nor need we visit on the child's constitution the sins inherent in the vaccine virus.

That pyæmia occasionally follows vaccination I suppose no one is prepared to deny. I have myself known two fatal cases of blood poisoning due directly to this cause; while statistics show that deaths from this cause per million births have increased from 155 before compulsory vaccination to 180 since.

That tubercle or scrofula can be engendered or intensified by vaccination is no new theory. DR. SQUIRRELL, an anti-vaccinator, suggested it 70 years ago, and now that a belief in the inoculability of tubercle is gaining ground, it will probably not be long before this danger is considered as real as that of vaccino-syphilis. PROFESSOR COHNHEIM declares that the test for tubercle is simply this, that the virus inoculated on a guinea pig will produce tubercle. Now, WILSON FOX has shown that vaccine lymph inoculated on a guinea pig does produce tuberculosis; *ergo*, vaccine lymph is tubercle. Again, the equine analogue of scrofula is glanders, farcy, or grease, three varieties of the same thing, and this according to JENNER, was the source of "the true and not the spurious cow-pox." So that the Jennerian lymph, which is still in use, and has passed through countless constitutions, is surely not the last thing in the world to be suspected of disseminating scrofulous disease.

As to figures to corroborate these statements, here they are.

Deaths under one year per million births from:—

	Scrofula.	Mesenteric disease.
Vaccination voluntary, 1847 to 1853	351	2,981
Vaccination obligatory, 1853 to 1867	611	3,371
Vaccination enforced, 1867 to 1878	908	4,373

These figures are taken from a Parliamentary return, No. 392, 1880.—*St. Bartholomew's Hospital*, Sep. 10th, 1881.

MR. ERNEST HART, M.R.C.S.

The PRESIDENT remarked that the medical profession had reasons for coming to the conclusion that, during the last thirteen years, their impressions as to the value of humanized lymph had undergone considerable change.—*British Medical Journal*, Sep. 24, 1881.

DR. W. B. CARPENTER, M.D.

It is unfortunately too true that with the reduction of small-pox mortality (by vaccination), there has been an increase in the mortality from measles and scarlatina, exceeding that which increase of population would account for; the number of deaths in England and Wales from the former of these diseases frequently exceeding 10,000 in the year; while the annual mortality from the latter averages nearly 20,000, sometimes exceeding 30,000.—*Nineteenth Century*, Oct. 1881. P. 547.

Dr. WALZ, City Councillor, Frankfort on the Oder.

It is now no longer denied that syphilis lying latent in young children, cannot always be detected by the most careful doctor ; but we are told that the cases of vaccinal syphilis are very few, and the risk very slight. We reply, that in these days syphilis is, apparently, one of the commonest complaints, that lymph is probably extensively impregnated with it ; that the transmission by vaccination is in all likelihood much more common than is generally imagined, and that the observed cases much more numerous than the acknowledged ones. Are we not justified by the laws of analogy in maintaining the possibility of the transmission in vaccination of other diseases, in addition to syphilis and scrofula ?—*Discourse on the occasion of the Cologne Congress of* Oct., 1881.

Dr. H. SCHOPPE, Bonn.

Sometimes children with good constitutions pass through the vaccine fever harmless, but in others it is an excitant of maladies of life-long duration. Medical men, I am sorry to say, have no sound knowledge on these important matters, and are kept in ignorance through prejudice.—*From Address delivered before the Cologne International Anti-Vaccination Congress, October*, 1881.

Dr. CHARLES PIGEON, Fourchambault, (Nievre,) France.

In an address delivered before the International Anti-Vaccination Congress at Cologne, Oct. 10th, 1881, Dr. Pigeon established the following propositions :—

1st.—That variola is not relatively a serious disorder, and that vaccination is no protection against it, but renders it more dangerous.

2nd.—That vaccination exposes the vaccinated to syphilis.

3rd.—That vaccination exposes the vaccinated to several other diseases, and is the means of exciting sundry others, the major part of which are more dangerous than small-pox.

4th.—That vaccination is a powerful cause of the degeneration of mankind.

*Dr. HUBERT BOENS, Charleroi, 1881.

It is not difficult to prove that vaccination is an evil, *per se*, and the fruitful cause of disease and death to many thousands in all countries. Sometimes the evil is apparent, but often the seeds are sown in the system, and the diseases are not manifested for some

years. Vaccination undermines the constitution, and if re-vaccination now demanded by the medical profession be persisted in, the entire community must become physically degenerate.

In their mischievous effects, the vaccine lymphs are alike, whether obtained from children or from calves. The one is too often taken from the classes subject to syphilis and scrofula, the once-dreaded "king's evil;" the other is specially liable to convey lung complaint; and the peculiar morbid phenomena excited in the vaccinated patients is the compound result of whatever disease exists in their constitution, and the special fermentation caused by the addition of the vaccine complaint. VERDE DE LISLE, ANCELON, CARNOT, and others, have statistically shown that universal vaccination bodes universal deterioration of the human species; that it augments the mortality of infancy and youth; that it has doubled the deaths in the military hospitals; increased the number and fatality of small-pox epidemics; and rendered its adherents specially subject to diseases of a typhoid character. In short, the more a nation is vaccinated, the more it will suffer from each zymotic epidemic, and the more rapid will be its physical decline—From *the closing address delivered before the 2nd International Anti-Vaccination Congress at Cologne*, Oct. 12th, 1881.

DR. BRERETON, Sydney, New South Wales, 1881.

In my experience, I have seen more evils result from vaccination than I ever saw from small-pox. I have seen direct fatal results from vaccination. I have seen chronic—incurably chronic—disease the result of vaccination, and death after the lapse of many years; and I have seen diseases of a destructive character introduced into the system through vaccination. Small-pox has steadily increased and is increasing, as the practice of vaccination is more generally enforced.—*Evidence given before the Cabinet and Legislature at Sydney.* From *The Sydney Morning Herald*, Oct. 25th, 1881.

DR. FORTESCUE, Sydney, New South Wales.

There are cases in which children having some inherent delicacy of constitution, only wait for some depressing cause to develop symptoms of disease, and no doubt vaccination sometimes acts as the depressing cause, and the children are made ill in consequence of that depression, and indirectly by the process of Vaccination. —*Sydney Morning Herald*, Oct. 25th, 1881.

Dr. E. M. RIPLEY, Physician and Surgeon, Unionville, Conn. U.S.A.

Vaccination is a fraud and a crime, and I cannot conscientiously lend it my support for the sake of gain. I have positively refused to vaccinate for four years past, and the longer I live, the greater is my detestation of it. It does not protect, and it does endanger, health and life.—*Letter to* A. E. Giles, Esq. Barrister-at-Law, Hyde Park, Mass., U.S. Nov. 2nd, 1881.

J. A. McMUNN, M.B., L.R.C.S., &c.

Every newspaper is studded with advertisements inviting the public to purify and renovate their blood at a shilling a bottle, while Poor-law vaccinators are labouring industriously to vitiate and contaminate the same at the rate of two shillings per case. All who are vaccinated do not contract loathsome diseases, we are informed. All who enter the battlefield are not slain, but the liability and risk in both cases are essentially similar; whoever escapes has reason to be thankful. In order to avert disease, decomposing animal matter is made to permeate the system. The result is what any rational being might anticipate. "As you sow, so must you reap." If you disseminate the germs of disease, you will in due season reap.—*Belfast Telegraph*, Nov. 9th, 1881.

Dr. LUDINGTON, New Britain, Conn. U.S.

Gave an instance in which leprosy had been communicated to the patient by vaccination. He cited cases where the same person had small-pox repeatedly; and affirmed his conviction that if variola could not prevent its own recurrence, it was futile to seek such prevention by other disorders.—*Meeting of Eclectic Medical Association*, Nov. 15th, 1881.

Dr. PEASE, Thomaston, U.S.

Said he had been employed in Government service in the army during the civil war. Part of his duty was to vaccinate. The soldiers would be drawn up in line and compelled to bare their arms for him to operate. Some of the sores thus produced were frightful. The arm would swell to inordinate dimensions, even endangering the life of many. Yet it kept off no pestilence; and he could declare from his own experience and observation that vaccination was the veriest humbug imaginable.—*Eclectic Medical Association*, Meeting, Nov. 15th, 1881.

* Dr. FISK, of Guildford, U.S.

Spoke of the liability to transmit other disorders with the vaccine virus. It was notorious, he said, that a large number of the animals slaughtered by butchers had diseased lungs and livers. The fact was carefully kept out of sight, but such is the case. Bovine virus taken from such animals would convey the other diseases with it. Scrofula and consumption are so propagated.—*Eclectic Medical Association*, New Haven, Conn., U.S., Nov. 15th, 1881.

* Dr. S. B. MUNN, of Waterbury, Connecticut, U.S.

Reviewed the history of vaccination, and combated the pretence that it would protect against small-pox. He declared that if a law should be passed to make medical men pecuniarily responsible for the ill effects, no physician would ever vaccinate. He showed what these effects were. Vaccine virus induces a ferment in the blood, with an active tendency towards the formation of pus; erysipelas was liable to intervene. As for protection, there was none whatever. Jenner himself, after several patients had taken small-pox, declared that cow-pox virus was not a prophylactic against attack; but that virus from the heels of a diseased horse was the only safeguard. —From *Address delivered before Eclectic Medical Association*, Nov. 15th, 1881.

CONNECTICUT ECLECTIC MEDICAL ASSOCIATION.

The Association adopted the following resolution by a unanimous vote:—

Resolved, That the Eclectic Medical Association of Connecticut hereby declares its convictions against the practice of Vaccination and all legislation making it compulsory; and asks the Legislatures of the several States to pass laws prohibiting Sanitary Boards, School Boards, and other local authorities, from making and enforcing regulations for that purpose.—Reported by Prof. Alex. Wilder, M.D., for *The Vaccination Inquirer and Health Review*, Nov. 15th, 1881.

T. H. HAYLE, M.B., Lond.

I believe vaccination from human beings to be wrong. In this age, when the natural laws of health are totally disregarded by most people, and immorality so common, we can never be sure that the blood of a child is in a pure state. When great care is taken you

can generally discover syphilis, if present, but it is a totally different matter as regards scrofula. Very often scrofula lies dormant in the blood of the child until it grows up, when it breaks out with consumption or some kindred disease. The handsomest and prettiest and healthiest-looking children are sometimes the most scrofulous. But it is said that scrofula in the blood does not cause bad results from vaccination, but for my part I would not like to be vaccinated from a person in consumption, and the poison in the blood is the same whether the consumption has broken out or not. And it stands to reason that scrofulous blood cannot generate such good vaccine matter as pure blood, therefore until the human race becomes perfectly healthy, I would do away with vaccination from human beings entirely, and use only pure calf lymph, drawn from healthy and cleanlily-kept calves, living as far as possible according to the laws of nature; against such vaccination I think there can be no objection.

But how is it that the bad effects of scrofula, following vaccination, have been overlooked? It may be explained in this way, and I think satisfactorily. Scrofula, even in those who have it in their blood from birth, very often does not show itself till nearly adult age; this, I believe, is admitted by all. If this is so, how can inoculated scrofula break out sooner? I should say it would take longer. Being vaccinated from a scrofulous child fully explains how one child in a healthy family may break out with scrofula or consumption, although this child may have been under quite as favourable circumstances of health as the others. This being true, what has vaccination done? It has brought disease, sickness, sorrow, and death, into healthy and innocent families.—*Rochdale Observer*, Dec. 3rd, 1881.

Dr. J. SUTHERLAND, Ashton New Road, Manchester.

At the inquest held on the body of William Henry Carpenter, who was vaccinated a month ago, said the deceased was brought to him on the 7th inst. There were five distinct vaccination marks upon the arm. Erysipelas had then begun, and had extended to the body. He visited the child every day until death. He had made a *post-mortem* examination, and found the organs healthy, with the exception that there was congestion of the lung, which, he expected, followed the erysipelas. Vaccination was sometimes followed by "breaking out." He saw nothing to lead him to think that vaccination had not been properly performed. He considered that as legislation made vaccination compulsory, some compensation should be made when there were results as in the present case. He did not belong to the anti-vaccination party. The jury returned a verdict to the effect that death resulted from erysipelas caused by vaccination.—*Manchester Guardian*, Dec. 20th, 1881.

The STUDENTS' JOURNAL & HOSPITAL GAZETTE, January 14th, 1882.

Many deaths have undoubtedly resulted from vaccination, and an unknown number of children have had their constitutions cruelly injured through vaccination with lymph from a syphilitic child.

T. MACKENZIE, M.D., F.R.C.P., Edin., January 26th, 1882.

When I produce children of three different families, where scrofula was never heard of till they were vaccinated, but whose necks are now a sad sight to see. "Pooh! pooh! you got bad lymph for them, and must be more careful," is all the comfort I get.

Dr. HUSBAND.

It should be borne in mind that it cannot be shown that there is *no* risk of transmitting diseases from the calf to the infant. The very fact that vaccinia itself is so readily communicated, is a presumption that danger of this kind does exist—not probably greater than that of communicating disease from infant to infant, but, for anything we know, not less.—*From 35th Annual Report of Scottish Board of Health.*

RICHARD STONEHAM, M.D., Surgeon, Philadelphia College.

In the postscript of a letter which I wrote to one of the editors of our county paper some time ago, I observed that—"Her Majesty the Queen had been vaccinated, and that time would tell whether it was a wise experiment." I now hear that her Majesty has severely suffered from an abscess of the arm, a form of disease often following vaccination; showing that royalty is not exempt from afflictions of the human body when physiological laws are violated. I have often seen abscesses, glandular swellings, and skin diseases, follow the vaccine operation.—From *The Bridgwater Gazette.*

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N.B.—Those marked with an asterisk treat of Animal (Cow, Horse, or Calf) Lymph, without reference to injuries from arm to arm Vaccination.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all information needed to use ACAM2000 safely and effectively. See full prescribing information for ACAM2000.

ACAM2000, (Smallpox (Vaccinia) Vaccine, Live)

Lyophilized preparation for percutaneous scarification

Initial U.S. Approval: 2007

WARNING:
See full prescribing information for complete boxed warning

- **Myocarditis and pericarditis (suspect cases observed at a rate of 5.7 per 1000 primary vaccinees (95% CI: 1.9-13.3)), encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including STEVENS-JOHNSON SYNDROME), eczema vaccinatum resulting in permanent sequelae or death, ocular complications, blindness and fetal death, have occurred following either primary vaccination or revaccination with live vaccinia virus smallpox vaccines. These risks are increased in certain individuals and may result in severe disability, permanent neurological sequelae and/or death [see Warnings and Precautions (5)].**

----------INDICATIONS AND USAGE----------

ACAM2000® is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection.

----------DOSAGE AND ADMINISTRATION----------

- Administer ACAM2000 only after being trained on the safe and effective administration of the vaccine by the percutaneous route (scarification). (2.3)
- A droplet of ACAM2000 is administered by the percutaneous route (scarification) using 15 jabs of a bifurcated needle. ACAM2000 should not be injected by the intradermal, subcutaneous, intramuscular, or intravenous route. (2.3)
- The droplet (0.0025 mL) of reconstituted vaccine is picked up with a bifurcated needle by dipping needle into ACAM2000 vial. (2.3)
- See full prescribing information for instructions for vaccine preparation (2.2), administration including provision of the Medication Guide to vaccinees and instruction to vaccinees about vaccination site care, (2.3) and interpretation of response to vaccination. (2.4)
- Re-vaccination may be recommended (e.g. every 3 years). (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

- Lyophilized powder reconstituted with packaged diluent. After reconstitution, each vial has approximately 100 doses of 0.0025 mL of live vaccinia virus containing 2.5 – 12.5 x 10^5 plaque forming units. (3)

----------CONTRAINDICATIONS----------

- Individuals with severe immunodeficiency who are not expected to benefit from the vaccine. These individuals may include persons who are undergoing bone marrow transplantation or persons with primary or acquired immunodeficiency states who require isolation (4).

-- ----------WARNINGS AND PRECAUTIONS----------

- Myocarditis and/or pericarditis, ischemic heart disease and non-ischemic dilated cardiomyopathy. (5.1, 5.2)
- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome), eczema vaccinatum, fetal vaccinia and fetal death. (5.1)
- Ocular vaccinia and blindness. (5.3)
- These risks, including risks of severe disability and/or death, are increased in vaccinees with:
  - Cardiac disease (5.2).
  - Eye disease treated with topical steroids. (5.3)
  - Congenital or acquired immune deficiency disorders. (5.4)
  - History or presence of eczema and other skin conditions. (5.5)
  - Infants < 12 months of age. (5.6)
  - Pregnancy (5.7)
- ACAM2000 is a live vaccinia virus that can be transmitted to persons who have close contact with the vaccinee and the risks in contacts are the same as those stated for vaccinees. (5.10)

----------ADVERSE REACTIONS----------

Common adverse events include inoculation site signs and symptoms, lymphadenitis, and constitutional symptoms, such as malaise, fatigue, fever, myalgia, and headache (6.1). These adverse events are less frequent in revaccinated persons than persons receiving the vaccine for the first time.

Inadvertent inoculation at other sites is the most frequent complication of vaccinia vaccination. The most common sites involved are the face, nose, mouth, lips, genitalia and anus.

Self-limited skin rashes not associated with vaccinia replication in skin, including urticaria and folliculitis, may occur following vaccination.

To report SUSPECTED ADVERSE REACTIONS, contact Emergent BioSolutions at 1-877-246-8472 or VAERS at 800-822-7967 and https://vaers.hhs.gov.

----------USE IN SPECIFIC POPULATIONS----------

- ACAM2000 may rarely cause fetal infection, usually resulting in stillbirth or death. (8.1)
- ACAM2000 live vaccinia virus may be transmitted from a lactating mother to her infant causing complications in the infant from inadvertent inoculation. (8.3)
- ACAM2000 may be associated with an increased risk of serious complications in children, especially in infants younger than 12 months. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE

Revised: [03/2018]

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FULL PRESCRIBING INFORMATION

WARNING:

- Suspected cases of myocarditis and/or pericarditis have been observed in healthy adult primary vaccinees (at an approximate rate of 5.7 per 1000, 95% CI: 1.9-13.3) receiving ACAM2000 [see Warnings and Precautions (5.1)].
- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including STEVENS-JOHNSON SYNDROME), eczema vaccinatum resulting in permanent sequelae or death, ocular complications, blindness, and fetal death have occurred following either primary vaccination or revaccination with live vaccinia virus smallpox vaccines [see Warnings and Precautions (5)].
- These risks are increased in vaccinees with the following conditions and may result in severe disability, permanent neurological sequelae and/or death:
  - Cardiac disease or a history of cardiac disease
  - Eye disease treated with topical steroids
  - Congenital or acquired immune deficiency disorders, including those taking immunosuppressive medications
  - Eczema and persons with a history of eczema or other acute or chronic exfoliative skin conditions
  - Infants less than 12 months of age
  - Pregnancy

ACAM2000 is a live vaccinia virus that can be transmitted to persons who have close contact with the vaccinee and the risks in contacts are the same as those for the vaccinee.

The risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection.

1 INDICATIONS AND USAGE

ACAM2000® is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection.

2 DOSAGE AND ADMINISTRATION

Administer ACAM2000 only after being trained on the safe and effective administration of the vaccine by the percutaneous route (scarification). ACAM2000 should not be injected by the intradermal, subcutaneous, intramuscular, or intravenous route. Provide each patient with the FDA-approved Medication Guide prior to administering the vaccine.

2.1 Instructions for Vaccine Preparation

2.1.1 Reconstitution

ACAM2000 is reconstituted by addition of 0.3 mL of diluent to the vial containing lyophilized vaccine. **Note: this 0.3 mL of diluent is not the entire content of the diluent vial.** ACAM2000 should only be reconstituted with 0.3 mL of the diluent provided. The vaccine vial should be removed from cold storage and brought to room temperature before reconstitution. The flip cap seals of the vaccine and diluent vials are removed, and each rubber stopper is wiped with an isopropyl alcohol swab and allowed to dry thoroughly. Using aseptic technique and a sterile 1 mL syringe fitted with a 25 gauge x 5/8" needle (provided), draw up 0.3 mL of diluent and transfer the entire content of the syringe to the vaccine vial. Gently swirl to mix but try not to get product on the rubber stopper. The reconstituted vaccine should be a clear to slightly hazy, colorless to straw-colored liquid free from extraneous matter. Reconstituted vaccine should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is observed, the vaccine should not be used and the vial should be disposed safely. [See Preparation / Handling Precautions and Instructions for Disposal (2.2)]

2.1.2 Storage following Reconstitution

After reconstitution, ACAM2000 vaccine may be administered within 6 to 8 hours if kept at room temperature (20-25°C, 68-77°F). Unused, reconstituted ACAM2000 vaccine may be stored in a refrigerator (2-8°C, 36-46°F) up to 30 days, after which it should be discarded as a biohazardous material. [See Preparation / Handling Precautions and Instructions for Disposal (2.2)] Exposure of reconstituted vaccine to room temperature during vaccination sessions should be minimized by placing it in refrigerator or on ice between patient administrations.

2.2 Preparation / Handling Precautions and Instructions for Disposal

Personnel preparing and administering the vaccine should wear surgical or protective gloves and avoid contact of vaccine with skin, eyes or mucous membranes.

The vaccine vial, its stopper, the diluent syringe, the vented needle used for reconstitution, the bifurcated needle used for administration, and any gauze or cotton that came in contact with the vaccine should be discarded in leak-proof, puncture-proof biohazard containers. These containers should then be disposed of appropriately.

2.3 Vaccination Instructions

The reconstituted vaccine should be brought to room temperature prior to administration. Before administration, the vial contents should be visually examined to verify the absence of particulates and gently swirled, without allowing the product to contact the rubber stopper, if necessary to re-dissolve any precipitates that might have formed.

The site of vaccination is the upper arm over the insertion of the deltoid muscle.

No skin preparation should be performed unless the skin at the intended site of vaccination is obviously dirty, in which case an alcohol swab(s) may be used to clean the area. If alcohol is used, the skin must be allowed to dry thoroughly to prevent inactivation of the live vaccine virus by the alcohol.

Remove the vaccine vial cap. Remove bifurcated needle from individual wrapping. Submerge bifurcated end of needle in reconstituted vaccine solution. The needle will pick up a droplet of vaccine (0.0025 mL) within the fork of the bifurcation. Use aseptic technique, i.e., do not insert the upper part of the needle that has been in contact with fingers into the vaccine vial, and never re-dip the needle into the vaccine vial if the needle has touched skin.

Deposit the droplet of vaccine onto clean, dry skin of the arm prepared for vaccination. The needle is held between thumb and first finger perpendicular to the skin. The wrist of the hand holding the needle of the vaccinator rests against the patient's arm. Rapidly make 15 jabs of the needle perpendicular to the skin through the vaccine droplet to puncture the skin, within a diameter of about 5 mm. The jabs should be vigorous enough so that a drop of blood appears at the vaccination site.

Any excess droplets of vaccine and blood should be wiped off the skin using a dry gauze pad and discarded in a biohazard container. Discard the needle in a biohazard sharps container. Close the vaccine vial by reinserting the rubber cap and return to a refrigerator or place on ice unless it will be used immediately to vaccinate another subject. [See Storage Following Reconstitution (2.1.2)]

Cover the vaccination site loosely with a gauze bandage, using first aid adhesive tape to keep it in place. This bandage provides a barrier to protect against spread of the vaccinia virus. If the vaccinee is involved in direct patient care, the gauze should be covered with a semipermeable (semiocclusive) dressing as an additional barrier. A semipermeable dressing is one that allows for the passage of air but does not allow for the passage of fluids.

Wash hands with soap and warm water or with alcohol-based hand rubs such as gels or foams after direct contact with the vaccination site, the bandage or clothes, towels or sheets that might be contaminated with virus from the vaccination site. This is vital in order to remove any virus from your hands and prevent contact spread.

Put the contaminated bandages in a sealed plastic bag and throw them away in the trash.

Wash separately clothing, towels, bedding or other items that may have come in direct contact with the vaccination site or drainage from the site, using hot water with detergent and/or bleach. Wash hands afterwards.

Don't use a bandage that blocks air from the vaccination site. This may cause the skin at the vaccination site to soften and wear away. Use loose gauze secured with medical tape to cover the site.

Don't put salves or ointments on the vaccination site.

2.4 Instructions for Interpreting Vaccination Response

2.4.1 Primary Vaccinees

In an individual vaccinated for the first time (primary vaccination), the expected response to vaccination is the development of a major cutaneous reaction (characterized by a pustule) at the site of inoculation. The lesion evolves gradually, with appearance of a papule at the site of vaccination after 2-5 days. The papule becomes vesicular, then pustular, and reaches its maximum size at 8-10 days after vaccination. The pustule dries and forms a scab, which usually separates within 14-21 days, leaving a pitted scar. (See Figure 1) Formation of a major cutaneous reaction by day 6-8 is evidence of a successful 'take' and acquisition of protective immunity. An equivocal reaction is any reaction that is not a major reaction, and indicates a non-take (vaccination failure) due to impotent vaccine or inadequate vaccination technique.

2.4.2 Previously Vaccinated Individuals (Revaccination)

Successful vaccination in an individual previously exposed to vaccine is confirmed when a major cutaneous reaction [See Primary Vaccinees (2.4.1) and Figure 1] is observed 6 to 8 days post-vaccination. However any prior vaccination may modify (reduce) the cutaneous response upon revaccination (Figure 2) such that the absence of a cutaneous response does not necessarily indicate vaccination failure. Previously vaccinated individuals who do not have a cutaneous response on revaccination do not require revaccination to try to elicit a cutaneous response.

2.4.3 Vaccination Failures

Individuals who are not successfully vaccinated (i.e., vaccination failures) after primary vaccination may be revaccinated again in an attempt to achieve a satisfactory take. The vaccination procedures should be checked, and vaccination repeated with vaccine from another vial or vaccine lot, employing the same technique described in 2.3 [See Vaccination Instructions (2.3)].

If a repeat vaccination is conducted using vaccine from another vial or vaccine lot fails to produce a major reaction, healthcare providers should consult the Centers for Disease Control and Prevention (CDC) Emergency Operations Center (EOC) at 770-488-7100and their state or local health department before giving another vaccination.

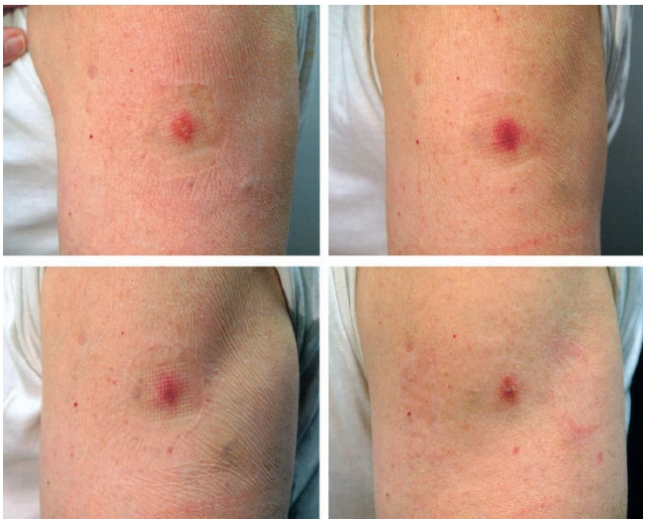
Figure 1: Progression of major cutaneous reaction after primary vaccination[1]

Day 5 **Day 8**

Day 10 **Day 14**

Figure 2: Progression of major cutaneous reaction after revaccination[1]

Day 3 **Day 7**



Day 10 **Day 14**

2.5 Booster Schedule

Persons at continued high risk of exposure to smallpox (e.g., research laboratory workers handling variola virus) should receive repeat ACAM2000 vaccination every three years.

2.6 Smallpox Vaccination Recommendations from US Government Agencies

Additional information may be obtained from U.S. Department of Defense (http://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodd/620503p.pdf) and U.S. Centers for Disease Control and Prevention (CDC) about smallpox vaccination (https://www.cdc.gov/smallpox/clinicians/vaccination.html).

3 DOSAGE FORMS AND STRENGTHS

After reconstitution of the lyophilized preparation, each vial has approximately 100 doses of 0.0025 mL of vaccinia virus (live) containing 2.5-12.5x10^5 plaque forming units / dose.

4 CONTRAINDICATIONS

There are very few absolute contraindications to this vaccine for those who are at high risk for smallpox. The risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection. See *Warnings and Precautions* (5) for persons who are at higher risk of experiencing serious vaccination complications.

Severe Immune Deficiency

Severe localized or systemic infection with vaccinia (progressive vaccinia) may occur in persons with weakened immune systems. Individuals with severe immunodeficiency who are not expected to benefit from the vaccine should not receive ACAM2000. These individuals may include individuals who are undergoing bone marrow transplantation or individuals with primary or acquired immunodeficiency who require isolation.

5 WARNINGS AND PRECAUTIONS

Persons at greatest risk of experiencing serious vaccination complications are often those at greatest risk for death from smallpox. The risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection.

5.1 Serious Complications and Death

Serious complications that may follow either primary live vaccinia smallpox vaccination or revaccination include: myocarditis and/or pericarditis, encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome), eczema vaccinatum, blindness, and fetal death in pregnant women. These complications may rarely lead to severe disability, permanent neurological sequelea and death. Based on clinical trials, symptoms of suspected myocarditis or pericarditis (such as chest pain, raised troponin/cardiac enzymes, or ECG abnormalities) occur in 5.7 per 1000 primary vaccinations. This finding includes cases of acute symptomatic or asymptomatic myocarditis or pericarditits or both. Historically, death following vaccination

with live vaccinia virus is a rare event; approximately 1 death per million primary vaccinations and 1 death per 4 million revaccinations have occurred after vaccination with live vaccinia virus. Death is most often the result of sudden cardiac death, postvaccinial encephalitis, progressive vaccinia, or eczema vaccinatum. Death has also been reported in unvaccinated contacts accidentally infected by individuals who have been vaccinated.

5.1.1 Incidence of Serious Complications in 1968 US Surveillance Studies

Estimates of the risks of occurrence of serious complications after primary vaccination and revaccination, based on safety surveillance studies conducted when live vaccinia virus smallpox vaccine (i.e., New York City Board of Health strain, Dryvax®) was routinely recommended, are as follows:

Table 1A - Rates of reported complications[(a)] associated with primary vaccinia vaccinations (cases/million vaccinations)[(b)]

Age (yrs)	<1	1-4	5-19	≥20	Overall rates[(h)]
Inadvertent inoculation[(c)] §	507.0	577.3	371.2	606.1	**529.2**
Generalized vaccinia	394.4	233.4	139.7	212.1	**241.5**
Eczema vaccinatum	14.1	44.2	34.9	30.3	**38.5**
Progressive vaccinia[(d)]	--[(g)]	3.2	--[(g)]	--[(g)]	**1.5**
Post-vaccinial encephalitis	42.3	9.5	8.7	--[(g)]	**12.3**
Death[(e)]	5	0.5	0.5	unknown	--
Total[(f)]	1549.3	1261.8	855.9	1515.2	**1253.8**

a. See article for descriptions of complications.
b. Adapted from Lane JM, Ruber FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys. J Infect Dis. 1970; 122:303-309.
c. Referenced as accidental implantation.
d. Referenced as vaccinia necrosum.
e. Death from all complications.
f. Rates of overall complications by age group include complications not provided in this table, including severe local reactions, bacterial superinfection of the vaccination site, and erythema multiforme.
g. No instances of this complication were identified during the 1968 10 state survey.
h. Overall rates for each complication include persons of unknown age.

Table 1B - Rates of reported serious complications[(a)] associated with vaccinia revaccinations (cases/million vaccinations)[(b)]

Age (yrs)	<1	1-4	5-19	≥20	Overall rates[(b)]
Inadvertent inoculation[(c)]	[(g)]	109.1	47.7	25.0	**42.1**
Generalized vaccinia	[(g)]	[(g)]	9.9	9.1	**9.0**
Eczema vaccinatum	[(g)]	[(g)]	2.0	4.5	**3.0**
Progressive vaccinia[(d)]	[(g)]	[(g)]	[(g)]	6.8	**3.0**
Post-vaccinial encephalitis	[(g)]	[(g)]	[(g)]	4.5	**2.0**
Death[(e)]	--	--	--	--	--
Total[(f)]	[(g)]	200.0	85.5	113.6	**108.2**

See Table 1A for explanation of footnotes.

5.1.2 Incidence of Serious Complications and Emergence of Myocarditis and/or Pericarditis in 2002-2005

Data on the incidence of adverse events among U.S. military personnel and civilian first responders vaccinated with Dryvax®, a licensed live vaccinia virus smallpox vaccine, during vaccination programs initiated in December 2002 are shown below in Table 2. The incidence of preventable adverse events (eczema vaccinatum, contact transmission, and auto-inoculation) were notably lower in these programs when compared with data collected in the 1960s; presumably because of better vaccination screening procedures and routine use of protective bandages over the inoculation site. Myocarditis and pericarditis were not commonly reported following smallpox vaccination in the 1960s, but emerged as a more frequent event based on more active surveillance in the military and civilian programs.

Table 2 - Serious adverse events in 2002-2005 [5]

Adverse event	N[a]	Incidence/ million	N[b]	Incidence/million
Myo/pericarditis	86	117.71	21	519.52
Post-vaccinal encephalitis	1	1.37	1	24.74
Eczema vaccinatum	0	0.00	0	0.00
Generalized vaccinia	43	58.86	3	74.22
Progressive vaccinia	0	0.00	0	0.00
Fetal vaccinia	0	0.00	0	0.00
Contact transmission	52	71.18	0	0.00
Auto-inoculation (non-ocular)	62	84.86	20	494.78
Ocular vaccinia	16	21.90	3	74.22

a. Department of Defense program (n=730,580) as of Jan05 where 71% primary vaccination; 89% male; median age 28.5 yr
b. Department of Health and Human Services program (n=40, 422) as of Jan04 where 36% primary vaccination; 36% male; median age 47.1 yr

5.1.3 Myocarditis and Pericarditis in the ACAM2000 Clinical Trial Experience

In clinical trials involving 2983 subjects who received ACAM2000 and 868 subjects who received Dryvax®, ten (10) cases of suspected myocarditis [0.2% (7 of 2983) ACAM2000 subjects and 0.3% (3 of 868) Dryvax® subjects] were identified. The mean time to onset of suspected myocarditis and/or pericarditis from vaccination was 11 days, with a range of 9 to 20 days. All subjects who experienced these cardiac events were naïve to vaccinia. Of the 10 subjects, 2 were hospitalized. None of the remaining 8 cases required hospitalization or treatment with medication. Of the 10 cases, 8 were sub-clinical and were detected only by ECG abnormalities with or without associated elevations of cardiac troponin I. All cases resolved by 9 months, with the exception of one female subject in the Dryvax® group, who had persistent borderline abnormal left ventricular ejection fraction on echocardiogram. The best estimate of risk for myocarditis and pericarditis is derived from the Phase 3 ACAM2000 clinical trials where there was active monitoring for potential of myocarditis and pericarditis. Among vaccinees naïve to vaccinia, 8 cases of suspected myocarditis and pericarditis were identified across both treatment groups, for a total incidence rate of 6.9 per 1000 vaccinees (8 of 1,162). The rate for the ACAM2000 treatment group were similar: 5.7 (95% CI: 1.9-13.3) per 1000 vaccinees (5 of 873 vaccinees) and for the Dryvax® group 10.4 (95% CI: 2.1-30.0) per 1000 vaccinees (3 of 289 vaccinees). No cases of myocarditis and/or pericarditis were identified in 1819 previously vaccinated subjects. The long-term outcome of myocarditis and pericarditis following ACAM2000 vaccination is currently unknown.

5.2 Cardiac Disease

Ischemic cardiac events, including fatalities, have been reported following smallpox vaccination; the relationship of these events, if any, to vaccination has not been established. In addition, cases of non-ischemic, dilated cardiomyopathy have been reported following smallpox vaccination; the relationship of these cases to smallpox vaccination is unknown.

There may be increased risks of adverse events with ACAM2000 in persons with known cardiac disease, including those diagnosed with previous myocardial infarction, angina, congestive heart failure, cardiomyopathy, chest

pain or shortness of breath with activity, stroke or transient ischemic attack, or other heart conditions. In addition, subjects who have been diagnosed with 3 or more of the following risk factors for ischemic coronary disease: 1) high blood pressure; 2) elevated blood cholesterol; 3) diabetes mellitus or high blood sugar; 4) first degree relative (for example mother, father, brother, or sister) who had a heart condition before the age of 50; or 5) smoke cigarettes may have increased risks.

5.3 Ocular Complications and Blindness
Accidental infection of the eye (ocular vaccinia) may result in ocular complications including keratitis, corneal scarring and blindness. Patients who are using corticosteroid eye drops may be at increased risk of ocular complications with ACAM2000.

5.4 Presence of Congenital or Acquired Immune Deficiency Disorders
Severe localized or systemic infection with vaccinia (progressive vaccinia) may occur in persons with weakened immune systems, including patients with leukemia, lymphoma, organ transplantation, generalized malignancy, HIV/AIDS, cellular or humoral immune deficiency, radiation therapy, or treatment with antimetabolites, alkylating agents, high-dose corticosteroids (>10 mg prednisone/day or equivalent for ≥2 weeks), or other immunomodulatory drugs. The vaccine is contraindicated in individuals with severe immunodeficiency [See Contraindications (4)]. Vaccinees with close contacts who have these conditions may be at increased risk because live vaccinia virus can be shed and be transmitted to close contacts.

5.5 History or Presence of Eczema and Other Skin Conditions
Persons with eczema of any description such as, atopic dermatitis, neurodermatitis, and other eczematous conditions, regardless of severity of the condition, or persons who have a history of these conditions at any time in the past, are at higher risk of developing eczema vaccinatum. Vaccinees with close contacts who have eczematous conditions, may be at increased risk because live vaccinia virus can shed and be transmitted to these close contacts. Vaccinees with other active acute, chronic or exfoliative skin disorders (including burns, impetigo, varicella zoster, acne vulgaris with open lesions, Darier's disease, psoriasis, seborrheic dermatitis, erythroderma, pustular dermatitis, etc.), or vaccinees with household contacts having such skin disorders might also be at higher risk for eczema vaccinatum.

5.6 Infants (< 12 months of Age) and Children
ACAM2000 has not been studied in infants or children. The risk of serious adverse events following vaccination with live vaccinia virus is higher in infants. Vaccinated persons who have close contact with infants, e.g., breastfeeding, must take precautions to avoid inadvertent transmission of ACAM2000 live vaccinia virus to infants.

5.7 Pregnancy
ACAM2000 has not been studied in pregnant women. Live vaccinia virus vaccines can cause fetal vaccinia and fetal death. If ACAM2000 is administered during pregnancy, the vaccinee should be apprised of the potential hazard to the fetus [See Use in Specific Populations (8.1)]. Pregnant women who are close contacts of vaccinees may be at increased risk because live vaccinia virus can shed and be transmitted to close contacts.

5.8 Allergy to ACAM2000 Smallpox Vaccine or its Components
ACAM2000 contains neomycin and polymyxin B. Persons allergic to these components may be at higher risk for adverse events after vaccination.

5.9 Management of Smallpox Vaccine Complications
The CDC can assist physicians in the diagnosis and management of patients with suspected complications of vaccinia (smallpox) vaccination. Vaccinia Immune Globulin (VIG) is indicated for certain complications of vaccination live vaccinia virus smallpox vaccine. If VIG and/or other antivirals are needed or additional information is required, physicians should contact the CDC EOC at 770-488-7100, Monday through Friday 8 AM to 4:30 PM Eastern Standard Time; at other times call (404) 639-2888.

5.10 Prevention of Transmission of Live Vaccinia Virus
The most important measure to prevent inadvertent auto-inoculation and contact transmission from vaccinia vaccination is thorough hand washing after changing the bandage or after any other contact with the vaccination site.

Individuals susceptible to adverse effects of vaccinia virus, i.e., those with cardiac disease, eye disease, immunodeficiency states, including HIV infection, eczema, pregnant women and infants, should be identified and measures should be taken to avoid contact between those individuals and persons with active vaccination lesions.

Recently vaccinated healthcare workers should avoid contact with patients, particularly those with immunodeficiencies, until the scab has separated from the skin at the vaccination site. However, if continued contact with patients is unavoidable, vaccinated healthcare workers should ensure the vaccination site is well covered and follow good hand-washing technique. In this setting, a more occlusive dressing may be used. Semipermeable polyurethane dressings are effective barriers to shedding of vaccinia. However, exudate may accumulate beneath the dressing, and care must be taken to prevent viral spread when the dressing is changed. In addition, accumulation of fluid beneath the dressing may increase skin maceration at the vaccination site. Accumulation of exudate may be decreased by first covering the vaccination with dry gauze, then applying the dressing over the gauze. The dressing should be changed every 1-3 days [See Self Inoculation and Spread to Close Contacts (17.3) and Care of the Vaccination Site and Potentially Contaminated Materials (17.4)].

5.11 Blood and Organ Donation
Blood and organ donation should be avoided for at least 30 days following vaccination with ACAM2000.

5.12 Limitations of Vaccine Effectiveness
ACAM2000 smallpox vaccine may not protect all persons exposed to smallpox.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome) and eczema vaccinatum. Severe disability, permanent neurological sequelae, and/or death may occur. Death of unvaccinated individuals who have contact with vaccinated individuals. [See Warnings and Precautions (5.1)].
- Myocarditis and/or pericarditis, ischemic heart disease and non-ischemic, dilated cardiomyopathy [See Warnings and Precautions (5.1)].
- Ocular complications and blindness [See Warnings and Precautions (5.3)].

6.1 Overall Adverse Reaction Profile
Information regarding the safety of ACAM2000 has been derived from three sources: 1) ACAM2000 clinical trial experience (Phase 1, 2 and 3 clinical trials), 2) data compiled during the era of routine smallpox vaccination using other NYCBH vaccinia vaccines and 3) adverse event data obtained during military and civilian smallpox vaccination programs (2002-2005) that used Dryvax®, a licensed live vaccinia virus smallpox vaccine.

- General Disorders and Administrative Site Conditions: In the ACAM2000 clinical studies 97% and 92% of vaccinia-naïve and previously vaccinated subjects, respectively, experienced one or more adverse event. Common events included injection site reactions (erythema, pruritus, pain and swelling) and constitutional symptoms (fatigue, malaise, feeling hot, rigors and exercise tolerance decreased). Across all ACAM2000 studies 10% of vaccinia-naïve and 3% of previously vaccinated subjects experienced at least one severe adverse event (defined as interfering with normal daily activities).
- Nervous System Disorder: Overall, 50% and 34% of vaccinia-naïve subjects and previously vaccinated subjects, respectively, reported headaches in ACAM2000 studies. There have been reports of headache following smallpox vaccination which required hospitalization. Although <1% of the subjects in the ACAM2000 program experienced severe headaches, none required hospitalization.

  Neurological adverse events assessed among the 2002 - 2005 military (n=590,400) and DHHS (n=64,600) programs temporally associated with smallpox vaccination included headache (95 cases), non-serious limb paresthesias (17 cases) or pain (13 cases) and dizziness or vertigo (13 cases). Serious neurologic adverse events included 13 cases of suspected meningitis, 3 cases of suspected encephalitis or myelitis, 11 cases of Bell palsy, 9 seizures (including 1 death), and 3 cases of Guillain-Barre syndrome. Among these 39 events, 27 (69%) occurred in primary vaccinees and all but 2 occurred within 12 days of vaccination. There have also been cases of photophobia following smallpox vaccination, some of which required hospitalization.
- Musculoskeletal and Connective Tissue Disorders: Across all ACAM2000 studies, severe, vaccine-related myalgia was seen in 1% of vaccinia-naïve subjects and <1% of previously vaccinated subjects.

Other adverse events included back pain, arthralgia and pain in extremity and none occurred with a frequency of more than 2% in either the vaccinia-naïve or previously vaccinated populations.

- Blood and Lymphatic System Disorders: The only adverse event occurring at ≥5% in the ACAM2000 studies were lymph node pain and lymphadenopathy. The incidence of severe lymph node pain and lymphadenopathy was <1%.

- Gastrointestinal (GI) Disorders: Commonly reported GI disorders among ACAM2000-treated subjects included nausea and diarrhea (14%), constipation (6%), and vomiting (4%). Severe abdominal pain, nausea, vomiting, constipation diarrhea and toothache accounted for all the severe adverse events reported and occurred in <1% of subjects.

- Skin and Subcutaneous Tissue Disorders: Erythema and rash were noted in 18% and 8% of subjects respectively. In ACAM2000 subjects 1% of vaccinia-naïve and <1% of previously vaccinated subjects experienced at least one severe adverse event. With the exception of one case of contact dermatitis and one case of urticaria, erythema and rash accounted for all severe events.

  Generalized rashes (erythematous, papulovesicular, urticarial, folliculitis, nonspecific) are not uncommon following smallpox vaccination and are presumed to be hypersensitivity reactions occurring among persons without underlying illnesses. These rashes are generally self-limited and require little or no therapy, except among patients whose conditions appear to be toxic or who have serious underlying illnesses.

  Inadvertent inoculation at other body sites is the most frequent complication of vaccinia vaccination, usually resulting from autoinoculation of the vaccine virus transferred from the site of vaccination. The most common sites involved are the face, nose, mouth, lips, genitalia and anus. Accidental infection of the eye (ocular vaccinia) may result in ocular complications including, but not limited to, keratitis, corneal scarring and blindness.

  Major cutaneous reactions at the site of inoculation, characterized by large area of erythema and induration and streaking inflammation of draining lymphatics may resemble cellulitis. Benign and malignant lesions have been reported to occur at the smallpox vaccination site.

6.2 ACAM2000 Clinical Trial Experience

Two randomized, controlled, multi-center Phase 3 trials enrolled 2244 subjects that received ACAM2000 and 737 that received a comparison licensed live vaccinia virus vaccine, Dryvax®. Study 1 was conducted in male (66% and 63% for ACAM2000 and Dryvax®, respectively) and female (34% and 37% for ACAM2000 and Dryvax®, respectively) subjects who previously had not been vaccinated with smallpox vaccine (i.e., vaccinia-naïve subjects). The majority of subjects were Caucasian (76% and 71% for ACAM2000 and Dryvax®, respectively) and the mean age was 23 in both groups with an age range from 18-30 years. Study 2 was conducted in male (50% and 48% for ACAM2000 and Dryvax®, respectively) and female (50% and 52% for ACAM2000 and Dryvax®, respectively) subjects who had been vaccinated with smallpox vaccine >10 years previously (i.e., previously vaccinated subjects). The majority of subjects were Caucasian (78% for both groups) and the mean age was 49 years in both groups with an age range of 31 to 84 years.

6.2.1 Common Adverse Events Reported in ACAM2000 Clinical Program

Adverse events reported by ≥5% of subjects in either the ACAM2000 or the comparison treatment group during Phase 3 studies are presented by type of adverse events, by baseline vaccination status (vaccinia-naïve versus previously vaccinated) and by treatment group. Severe vaccine-related adverse events, defined as interfering with normal daily activities, in vaccinia-naïve subjects were reported by 10% of subjects in the ACAM2000 group and 13% in the comparison group. In the previously vaccinated subjects, the incidence of severe vaccine-related adverse events was 4% for the ACAM2000 groups and 6% for the comparison group.

Table 3 - Adverse Events Reported by ≥5% of Subjects in ACAM2000 or Dryvax®

	ACAM2000 N=873[b] n (%)	Dryvax® N=289[b] n (%)	ACAM2000 N=1371[c] n (%)	Dryvax® N=448[c] n (%)
At least 1 adverse event	**864 (99)**	**288 (100)**	**1325 (97)**	**443 (99)**
Blood and lymphatic system disorders	**515 (59)**	**204 (71)**	**302 (22)**	**133 (30)**
Lymph node pain[a]*	494 (57)	199 (69)	261 (19)	119 (27)
Lymphadenopathy	72 (8)	35 (12)	78 (6)	29 (6)
Gastrointestinal disorders	**273 (31)**	**91 (31)**	**314 (23)**	**137 (31)**
Nausea[a]	170 (19)	65 (22)	142 (10)	63 (14)
Diarrhea[a]	144 (16)	34 (12)	158 (12)	77 (17)
Constipation[a]	49 (6)	9 (3)	88 (6)	31 (7)
Vomiting[a]	42 (5)	10 (3)	40 (3)	18 (4)
General disorders and administration site conditions	**850 (97)**	**288 (100)**	**1280 (93)**	**434 (97)**
Injection site pruritus[a]	804 (92)	277 (96)	1130 (82)	416 (93)
Injection site erythema[a]	649 (74)	229 (79)	841 (61)	324 (72)
Injection site pain[a]	582 (67)	208 (72)	505 (37)	209 (47)
Fatigue[a]	423 (48)	161 (56)	468 (34)	184 (41)
Injection site swelling	422 (48)	165 (57)	384 (28)	188 (42)
Malaise[a]	327 (37)	122 (42)	381 (28)	147 (33)
Feeling hot[a]	276 (32)	97 (34)	271 (20)	114 (25)
Rigors[a]	185 (21)	66 (23)	171 (12)	76 (17)
Exercise tolerance decreased[a]	98 (11)	35 (12)	105 (8)	50 (11)
Musculoskeletal and connective tissue disorders	**418 (48)**	**153 (53)**	**418 (30)**	**160 (36)**
Myalgia[a]	404 (46)	147 (51)	374 (27)	148 (33)
Nervous system disorders	444 (51)	151 (52)	453 (33)	174 (39)
Headache[a]	433 (50)	150 (52)	437 (32)	166 (37)
Respiratory, thoracic, and mediastinal disorders	**134 (15)**	**40 (14)**	**127 (9)**	**42 (9)**
Dyspnea[a]	39 (4)	16 (6)	41 (3)	18 (4)
Skin and subcutaneous tissue disorders	**288 (33)**	**103 (36)**	**425 (31)**	**139 (31)**
Erythema[a]	190 (22)	69 (24)	329 (24)	107 (24)
Rash[a]	94 (11)	30 (10)	80 (6)	29 (6)

a. Event was listed on a checklist included in subject diaries; therefore should be considered solicited. In addition to events listed above the following were also included as part of the checklist: chest pain and heart palpitations, but these events did not occur in ≥5% of subjects.

b. Study 1 Vaccinia Naïve Subjects
   Study 2 Previously Vaccinated Subjects

7 DRUG INTERACTIONS

7.1 Simultaneous Administration with Other Vaccines

There are no data evaluating the simultaneous administration of ACAM2000 with other vaccines.

7.2 Interference with Laboratory Tests

ACAM2000 may induce false-positive tests for syphilis. Positive RPR tests results should be confirmed using a more specific test, such as the FTA assay.

ACAM2000 may induce temporary false-negative results for the tuberculin skin test (purified protein derivative [PPD]) and possibly, blood tests for tuberculosis. Tuberculin testing should be delayed if possible for 1 month following smallpox vaccination.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

ACAM2000 has not been studied in pregnant women. Live vaccinia virus vaccines can cause fetal harm when administered to a pregnant woman. Congenital infection, principally occurring during the first trimester, has been observed after vaccination with live vaccinia smallpox vaccines, although the risk may be low. Generalized vaccinia of the fetus, early delivery of a stillborn infant, or a high risk of perinatal death has been reported.

The only setting in which vaccination of pregnant women should be considered is when exposure to smallpox is considered likely. If this vaccine is used during pregnancy, or if the vaccinee lives in the same household with or has close contact with a pregnant woman, the vaccinee should be apprised of the potential hazard to the fetus. Healthcare providers, state health departments, and other public health staff should report to the National Smallpox Vaccine in Pregnancy Registry all pregnant women who, from 42 days prior to conception onward, received ACAM2000 or had close contact with a person who received ACAM2000 within the previous 28 days.. Civilian women should contact their healthcare provider or state health department for help enrolling in the registry. All civilian and military cases should be reported to the DoD, telephone 619 553-9255, Defense Switched Network (DSN) 553-9255, fax 619 533-7601 or e-mail NHRC-BirthRegistry@med.navy.mil**.**

8.3 Nursing Mothers

ACAM2000 has not been studied in lactating women. It is not known whether vaccine virus or antibodies are secreted in human milk. Live vaccinia virus can be inadvertently transmitted from a lactating mother to her infant. Infants are at high risk of developing serious complications from live vaccinia smallpox vaccination.

8.4 Pediatric Use

The safety and effectiveness of ACAM2000 have not been established in the age groups from birth to age 16. The use of ACAM2000 in all pediatric age groups is supported by evidence from the adequate and well-controlled studies of ACAM2000 in adults and with additional historical data with use of live vaccinia virus smallpox vaccine in pediatrics. Before the eradication of smallpox disease, live vaccinia virus smallpox vaccine was administered routinely in all pediatric age groups, including neonates and infants, and was effective in preventing smallpox disease. During that time, live vaccinia virus was occasionally associated with serious complications in children, the highest risk being in infants younger than 12 months of age. [See Warnings and Precautions (5.6)].

8.5 Geriatric Use

Clinical studies of ACAM2000 did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There are no published data to support the use of this vaccine in geriatric (persons >65 years) populations.

11 DESCRIPTION

ACAM2000, Smallpox (Vaccinia) Vaccine, Live, is a live vaccinia virus derived from plaque purification cloning from Dryvax® (Wyeth Laboratories, Marietta, PA, calf lymph vaccine, New York City Board of Health Strain) and grown in African Green Monkey kidney (Vero) cells and tested to be free of adventitious agents.

ACAM2000 is provided as a lyophilized preparation of purified live virus containing the following non-active excipients: 6-8 mM HEPES (pH 6.5-7.5), 2% human serum albumin USP, 0.5 – 0.7% sodium chloride USP, 5% mannitol USP, and trace amounts of neomycin and polymyxin B.

Diluent for ACAM2000 contains 50% (v/v) Glycerin USP, 0.25% (v/v) Phenol USP in Water for Injection USP, supplied in 3 mL clear glass vials containing 0.6 mL of diluent.

After reconstitution, each vial of ACAM2000 vaccine contains approximately 100 doses (0.0025 mL/dose). The concentration of vaccinia virus is 1.0-5.0 x 10^8 plaque-forming units (PFU)/mL or 2.5-12.5 x 10^5 PFU/dose determined by plaque assay in Vero cells. ACAM2000 is administered by the percutaneous route (scarification) using 15 jabs of a stainless steel bifurcated needle that has been dipped into the vaccine.

12 CLINICAL PHARMACOLOGY

Smallpox vaccine does not contain smallpox virus (variola) and cannot spread or cause smallpox.

12.1 Mechanism of Action

Vaccinia virus is a member of the same taxonomic group (the Orthopox genus) as smallpox (variola) virus, and immunity induced by vaccinia virus cross-protects against variola virus. Vaccinia virus causes a localized virus infection of the epidermis at the site of inoculation, surrounding dermal and subcutaneous tissues, and draining lymph nodes. Virus may be transiently present in blood and infects reticuloendothelial and other tissues. Langerhans cells in the epidermis are specific targets for the early stage of virus replication. The formation of a pustule (‘pock’ or ‘take’) at the site of inoculation provides evidence of protective immunity. The virus replicates within cells and viral antigens are presented to the immune system. Neutralizing antibodies and B and T cells provide long-term memory. The level of neutralizing antibody that protects against smallpox is unknown but >95% of persons undergoing primary vaccination develop neutralizing or hemagglutination inhibiting antibodies to vaccinia.

12.2 Pharmacodynamics

12.2.1 Cutaneous Response

The cutaneous responses following smallpox vaccination are dependent on the immune status of the individual, potency of the vaccine, and vaccination technique. Two types of responses have been defined by the WHO Expert Committee on Smallpox, and described by the Advisory Committee on Immunization Practices (ACIP). The responses include: a) major cutaneous reaction, which indicates that virus replication has taken place and vaccination was successful; or b) equivocal reaction. Equivocal reactions may be a consequence of pre-existing immunity adequate to suppress viral multiplication, vaccination technique failure, or use of inactive vaccine or vaccine that has lost potency.

Successful vaccination in persons who are naïve to smallpox vaccination, termed primary vaccination, is represented by a major cutaneous reaction, defined as a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion that might be a crust or an ulcer.

Subjects who have been previously vaccinated and are revaccinated may manifest a reduced cutaneous response compared to vaccinia-naïve subjects, but still exhibit an immune response to the vaccine. [See Dosage and Administration (2.4)]

12.2.2 Neutralizing Antibody and Cellular Immune Responses

Neutralizing antibodies are known to mediate protection against smallpox. Neutralizing antibodies against vaccinia develop in >95% of individuals following primary vaccination, rise rapidly (by day 15-20 after vaccination) and may be boosted on revaccination. Antibody titers are highly variable. Titers may remain high for longer periods following two or more vaccinations than after a primary vaccination. The level of the neutralizing antibody response following primary vaccination is generally in proportion to the intensity of the cutaneous reaction. The level of neutralizing antibody that is required to protect against smallpox has not been clearly established, although some studies indicate that persons with antibody titers > 1:32 are protected. Cellular immune responses are also elicited by vaccination and may contribute to protection and immunological memory.

12.2.3 Virus Shedding

Virus is shed from the vaccination site during the period starting with the development of a papule (day 2-5); shedding ceases when the scab separates and the lesion is re-epithelialized, about 14-21 days after vaccination. Steps should be taken in clinical use to reduce the risk of accidental infection of other sites in the vaccinated patient or of contact spread to other individuals [See Vaccination Instructions (2.3)].

14 CLINICAL STUDIES

Vaccine efficacy was assessed by comparing the immunologic response of ACAM2000 to another US-licensed live vaccinia virus smallpox vaccine, Dryvax®, in two randomized, multi-center active-controlled clinical trials; one study in subjects who previously had not been vaccinated with smallpox vaccine (i.e., vaccinia-naïve subjects) and one study in subjects who had been vaccinated with smallpox vaccine >10 years previously (i.e., previously

vaccinated subjects). In both trials, the co-primary efficacy endpoints were the proportion of subjects with a successful vaccination/revaccination and the geometric mean neutralizing antibody titer (GMT) on Day 30. Successful primary vaccination was defined as a major cutaneous reaction on Day 7 or 10 (Days 6 to 11, with allowable visit window). Successful revaccination was defined as development of any cutaneous lesion on Day 7 (± 1 day) of a measurable size. Successful revaccination was determined by a panel of experts who reviewed digital photographs of the cutaneous lesions.

The statistical method used to compare the proportion of subjects who were successfully vaccinated in the two treatment groups was a test of non-inferiority of ACAM2000 to the active comparator intended to rule out a greater than 5% margin of superiority of the comparator for successful primary vaccination (Study 1) and a 10% margin of superiority of the comparator for successful revaccination (Study 2). Non-inferiority was to be declared if the lower bound of the 1-sided 97.5% confidence interval (CI) for the percent difference between ACAM2000 and the comparator exceeded -5% in naïve subjects and -10% in previously vaccinated subjects.

Analysis of the GMT was performed using a test of non-inferiority of neutralizing antibody titer between ACAM2000 and the comparator, intended to ensure that the ratio of the GMTs of ACAM2000: comparator vaccine was at least 0.5 (equivalent to the difference of the $\log_{10}$ (GMT) being at least -0.301).

In Study 1, a total of 1037 male and female vaccinia-naïve subjects, aged 18 to 30 years inclusive, primarily Caucasian (76%) were randomized in a 3:1 ratio to receive ACAM2000 (780 subjects) or comparator (257 subjects). The ACAM2000 subjects were further stratified to receive one of three lots (Lots A, B and C) at a 1:1:1 ratio (258, 264, and 258 subjects, respectively). All subjects were to be evaluated for their cutaneous response and a random subset was selected for evaluation of neutralizing antibody response.

In Study 2, a total of 1647 male and female previously-vaccinated subjects, aged 31 to 84 years inclusive, primarily Caucasian (81%) were randomized in a 3:1 ratio to receive ACAM2000 (1242 subjects) or the comparator (405 subjects). The ACAM2000 subjects were further stratified to receive one of three lots (Lots A, B and C) at a 1:1:1 ratio (411, 417, and 414 subjects, respectively). All subjects were evaluated for their cutaneous response and a random subset was to be selected for evaluation of neutralizing antibody response.

Tables 4 and 5 present the results of the primary efficacy analyses for both studies.

Table 4 - Cutaneous Response (Vaccination Success) in Subjects Given ACAM2000 vs. Comparator Vaccine, Studies 1 and 2

	Study 1 ACAM 2000	**Study 1 Comparator**	**Study 2 ACAM 2000**	**Study 2 Comparator**
Size of Evaluable Population[a]	776	257	1189	388
Number of Vaccination Successes (%)	747 (96)[b]	255 (99)	998 (84)[d]	381 (98)
97.5% 1-sided CI by normal approx. on percent difference between ACAM2000-Comparator	-4.67% [c]	--	-17% [e]	--
Non-Inferiority to Comparator	Yes	--	No	--

a. Subjects who received study vaccine and were evaluated for a local cutaneous reaction within the protocol-designated timeframe were included in the efficacy evaluable (EE) population.
b. Results for vaccine lots, A, B and C were 95%, 98% and 96%.
c. Since the critical value for the evaluation was declared to be -5%, ACAM2000 is considered to be non-inferior to Comparator for this parameter.
d. Results for vaccine lots, A, B and C were 79%, 87% and 86%.
e. Since the critical value for the evaluation was declared to be -10%, ACAM2000 is not considered to be non-inferior to Comparator for this parameter.

Table 5 - Neutralizing Antibody Response in Subjects Given ACAM2000 vs. Comparator Vaccine, Studies 1 and 2

	Study 1 ACAM 2000	**Study 1 Comparator**	**Study 2 ACAM 2000**	**Study 2 Comparator**
Size of Evaluable Population[a]	565	190	734	376
GMT[b]	166	255	286	445
Log_{10} mean	2.2	2.4	2.5	2.6
97.5% 1-sided CI by ANOVA on difference between ACAM2000-Comparator	-0.307[c]	--	-0.275[d]	--
Meets Non-Inferiority to Comparator	No	--	Yes	--

a. A randomly selected sample of subjects who received study vaccine and had samples collected for neutralizing antibody response at Baseline and at the designated time-point post-treatment were included in the antibody evaluable (AnE) population.
b. GMT – Geometric mean neutralizing antibody titer as measured by Vaccinia 50% plaque reduction neutralization test.
c. Since the critical value for the evaluation was declared to be -0.301, ACAM2000 is not considered to be non-inferior to Comparator for this parameter.
d. Since the critical value for the evaluation was declared to be -0.301, ACAM2000 is considered to be non-inferior to Comparator for this parameter.

The primary determinant for an effective immune response in those naïve to vaccine is a major cutaneous reaction. ACAM2000 was non-inferior to comparator in this population with regard to eliciting a major cutaneous reaction. The measure of the strength of the generated antibody response was similar but did not meet the predefined criterion for non-inferiority. Among subjects who were previously vaccinated, development of a major cutaneous response after revaccination with vaccinia-based smallpox vaccines may not provide an accurate measure of the strength of the immune response because the pre-existing immunity modifies the scope of the cutaneous response. In previously vaccinated subjects, ACAM2000 was non-inferior to the comparator with regard to the strength of the neutralizing antibody immune response. Therefore, ACAM2000 was non-inferior to the comparator in the rate of major cutaneous reaction in those naïve to the vaccine, and the strength of the neutralizing antibody immune response in those previously exposed to vaccinia-based smallpox vaccines.

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16 HOW SUPPLIED / STORAGE AND HANDLING

16.1 How Supplied

ACAM2000, Smallpox (Vaccinia) Vaccine, Live, is supplied in multiple-dose 3 mL clear glass vials containing lyophilized powder (freeze-dried vaccine). After reconstitution with 0.3 mL of diluent, the vial contains approximately 100 nominal doses of 0.0025 mL of vaccinia virus (live), 1.0 - $5.0x10^8$ PFU/mL or 2.5-$12.5x10^5$ PFU/dose.

Diluent for ACAM2000, 50% (v/v) Glycerin USP, 0.25% (v/v) Phenol USP in Water for Injection USP, is supplied in 3 mL clear glass vials containing 0.6 mL of diluent.

Bifurcated needles are supplied in boxes (5 x 5 x 1 in) containing 100 needles.

1 mL tuberculin syringes with 25 gauge x 5/8" needles are supplied for vaccine reconstitution.

Both the vaccine and diluent vial stoppers are not made with natural rubber latex.

16.2 Storage and Handling

ACAM2000 should be stored in a freezer with an average temperature of -15°C to -25°C (+5°F to -13°F).

Prior to reconstitution, ACAM2000 vaccine retains a potency of $1.0x10^8$ PFU or higher per dose for at least 18 months when stored at refrigerated temperatures of +2-8°C (36-46°F).

During shipment, ACAM2000 should be maintained at a temperature of -10°C or colder.

After reconstitution, ACAM2000 vaccine may be administered during a 6 to 8 hour workday at room temperature (20-25°C, 68-77°F). Reconstituted ACAM2000 vaccine may be stored in a refrigerator (2-8°C, 36-46°F) no longer than 30 days, after which it should be discarded [*See Dosage and Administration (2.3)*]. Diluent for Smallpox Vaccine, (Vero Cells) Lyophilized, ACAM2000 should be stored at room temperature (15-30°C, 59-86°F).

ACAM2000 contains live vaccinia virus that is transmissible, and should be handled as an infectious agent once vials are open. See 2.1 [Instructions for Vaccine Preparation] and 2.2 [Preparation / Handling Precautions and Instructions for Disposal] for details on handling and disposal.

17 PATIENT COUNSELING INFORMATION

Please refer patient to the FDA-approved Medication Guide prepared for ACAM2000 Smallpox Vaccine.

17.1 Serious Complications of Vaccination

Patients must be informed of the major serious adverse events associated with vaccination, including myocarditis and/or pericarditis, progressive vaccinia in immunocompromised persons, eczema vaccinatum in persons with skin disorders, auto- and accidental inoculation, generalized vaccinia, urticaria, erythema multiforme major (including Stevens-Johnson syndrome) and fetal vaccinia in pregnant women.

17.2 Protecting Contacts at Highest Risk for Adverse Events

Patients must be informed that they should avoid contact with individuals at high risk of serious adverse effects of vaccinia virus, for instance, those with past or present eczema, immunodeficiency states including HIV infection, pregnancy, or infants less than 12 months of age.

17.3 Self-inoculation and Spread to Close Contacts

Patients must be advised that virus is shed from the cutaneous lesion at the site of inoculation from approximately Day 3 until scabbing occurs, typically between Days 14-21 after primary vaccination. Vaccinia virus may be transmitted by direct physical contact. Accidental infection of skin at sites other than the site of intentional vaccination (self-inoculation) may occur by trauma or scratching. Contact spread may also result in accidental inoculation of household members or other close contacts. The result of accidental infection is a pock lesion(s) at an unwanted site(s) in the vaccinee or contact, and resembles the vaccination site. Self-inoculation occurs most often on the face, eyelid, nose, and mouth, but lesions at any site of traumatic inoculation can occur. Self-inoculation of the eye may result in ocular vaccinia, a potentially serious complication.

17.4 Care of the Vaccination Site and Potentially Contaminated Materials

Patients must be given the following instructions:

- The vaccination site must be completely covered with a semipermeable bandage. Keep site covered until the scab falls off on its own.
- The vaccination site must be kept dry. Normal bathing may continue, but cover the vaccination site with waterproof bandage when bathing. The site should not be scrubbed. Cover the vaccination site with loose gauze bandage after bathing.
- Don’t scratch the vaccination site. Don’t scratch or pick at the scab.
- Do not touch the lesion or soiled bandage and subsequently touch other parts of the body particularly the eyes, anal and genital areas that are susceptible to accidental (auto-) inoculation.
- After changing the bandage or touching the site, wash hands thoroughly with soap and water or >60% alcohol-based hand-rub solutions.
- To prevent transmission to contacts, physical contact of objects that have come into contact with the lesion (e.g. soiled bandages, clothing, fingers) must be avoided.
- Wash separately clothing, towels, bedding or other items that may have come in direct contact with the vaccination site or drainage from the site, using hot water with detergent and/or bleach. Wash hands afterwards.
- Soiled and contaminated bandages must be placed in plastic bags for disposal.
- The vaccinee must wear a shirt with sleeves that covers the vaccination site as an extra precaution to prevent spread of the vaccinia virus. This is particularly important in situations of close physical contact.
- The vaccinee must change the bandage every 1 to 3 days. This will keep skin at the vaccination site intact and minimize softening.
- Don’t put salves or ointments on the vaccination site.
- When the scab fall off, throw it away in a sealed plastic bag and wash hands afterwards.

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(12) **United States Patent**
Friedman et al.

(10) **Patent No.: US 10,786,570 B2**
(45) **Date of Patent: Sep. 29, 2020**

(54) **FERRITIN NANOPARTICLE COMPOSITIONS AND METHODS TO MODULATE CELL ACTIVITY**

(71) Applicant: **The Rockefeller University**, New York, NY (US)

(72) Inventors: **Jeffrey Friedman**, New York, NY (US); **Sarah Stanley**, New York, NY (US)

(73) Assignee: **The Rockefeller University**, New York, NY (US)

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(Continued)

(58) **Field of Classification Search**
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(Continued)

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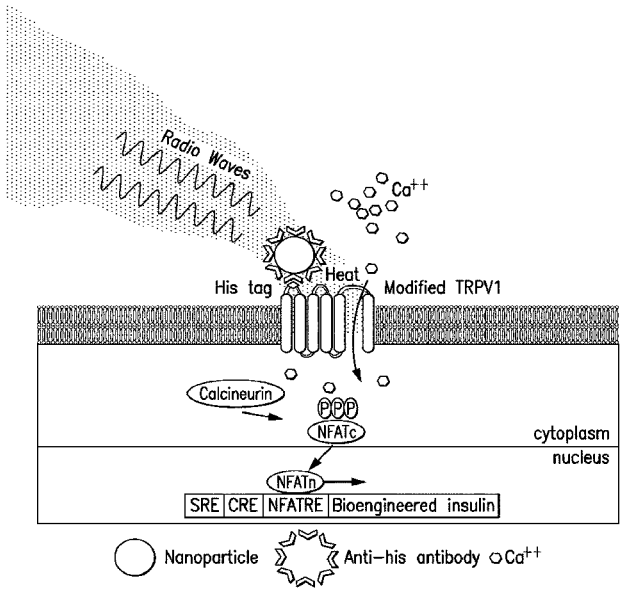
Primary Examiner — Carlos A Azpuru
(74) *Attorney, Agent, or Firm* — Hoffmann & Baron, LLP

(57) **ABSTRACT**

The present invention provides methods and compositions for the remote control of cell function based on the use of radiofrequency waves to excite nanoparticles targeted to specific cell types. The nanoparticles may be applied to the target cell extracellularly and/or expressed intracellularly. The cell type of interest expresses a temperature sensitive channel wherein excitation of the nanoparticles results in a localized temperature increase that is transduced into a cellular response. Such cellular responses may include, for example, increases in gene expression resulting in production of one or more physiologically active proteins. The expression of such proteins can be used to treat a variety of different inherited or acquired diseases or disorders in a subject. Accordingly, the invention provides a generic approach for treatment of any disease associated with a protein deficiency.

14 Claims, 56 Drawing Sheets



Related U.S. Application Data

continuation of application No. 14/239,427, filed as application No. PCT/US2012/052391 on Aug. 24, 2012, now Pat. No. 9,399,063.

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See application file for complete search history.

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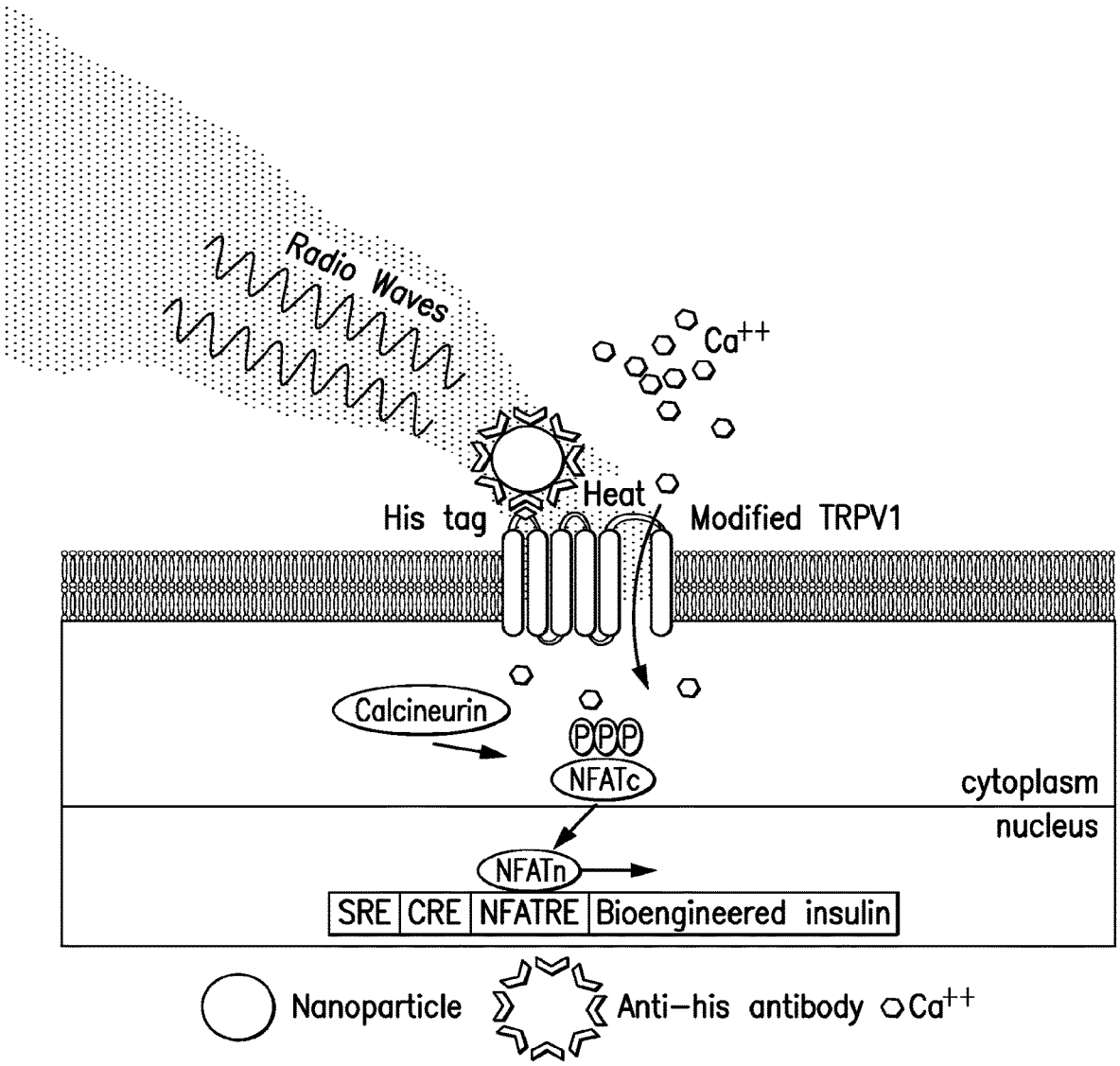
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NFATRE
Bioengineered insulin
Nanoparticle
Anti-his antibody
Ca++

FIG. 1

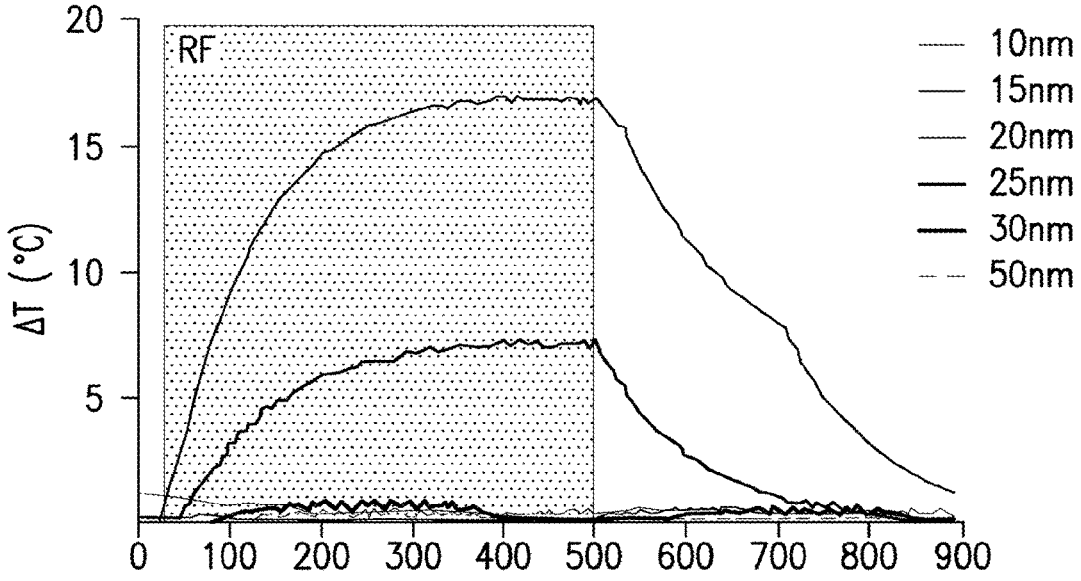

RF
10nm
15nm
20nm
25nm
30nm
50nm
ΔT (°C)
20
15
10
5
0
100
200
300
400
500
600
700
800
900

FIG. 2A

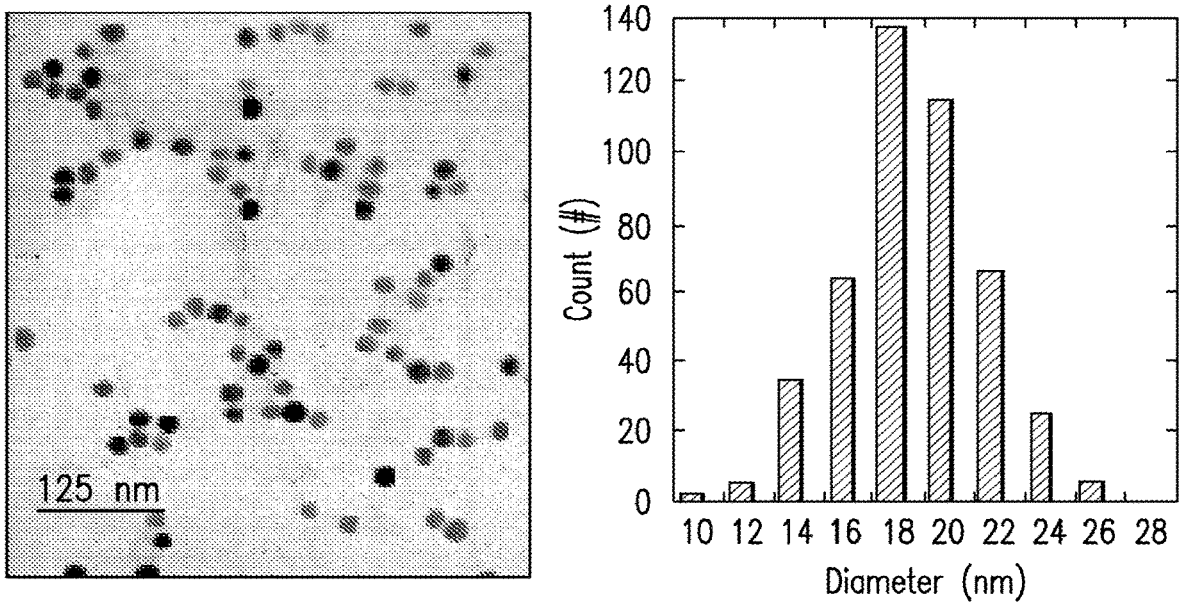
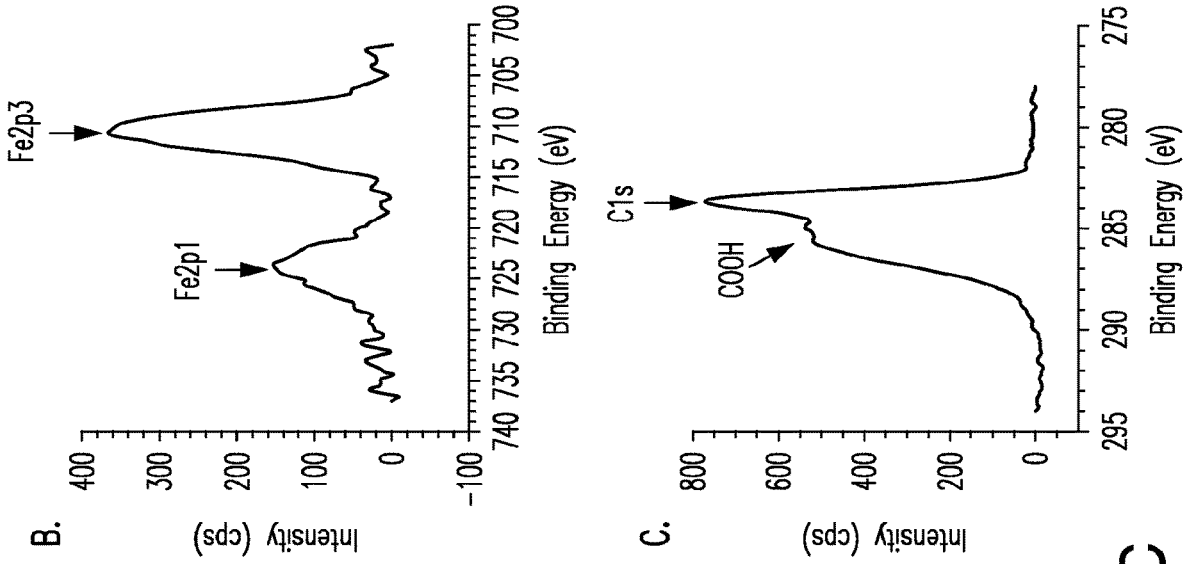

125 nm
Count (#)
140
120
100
80
60
40
20
0
10 12 14 16 18 20 22 24 26 28
Diameter (nm)

FIG. 2B


B.
Fe2p3
Fe2p1
Intensity (cps)
Binding Energy (eV)
C.
C1s
COOH
Intensity (cps)
Binding Energy (eV)

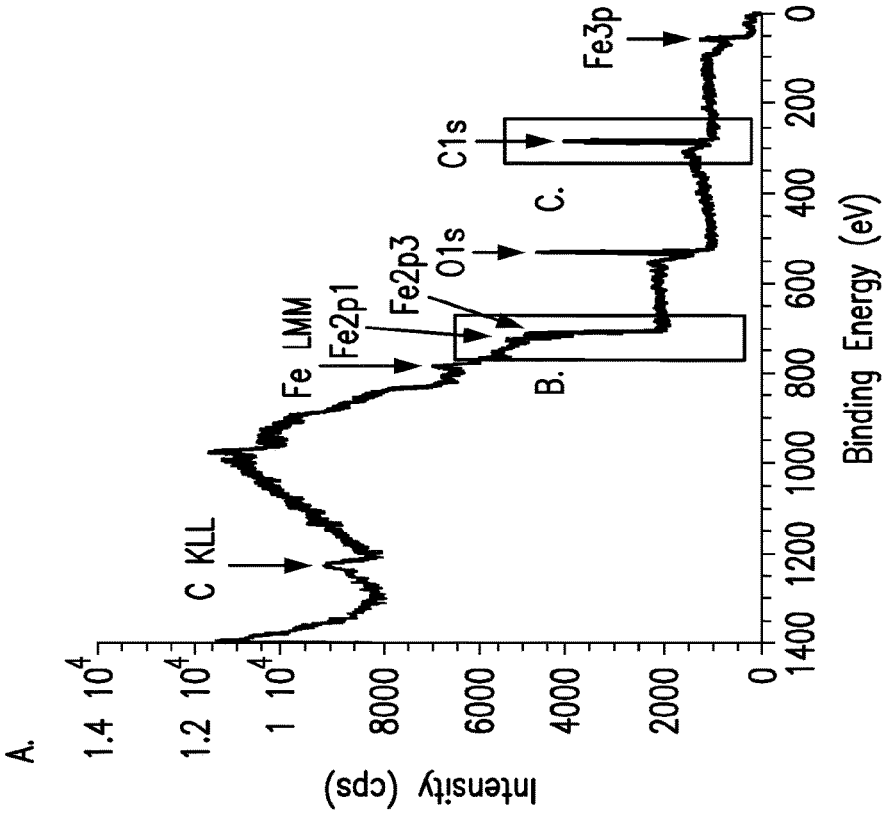

A.
C KLL
Fe LMM
Fe2p1
Fe2p3
O1s
C1s
Fe3p
B.
C.
Intensity (cps)
Binding Energy (eV)

FIG. 2C

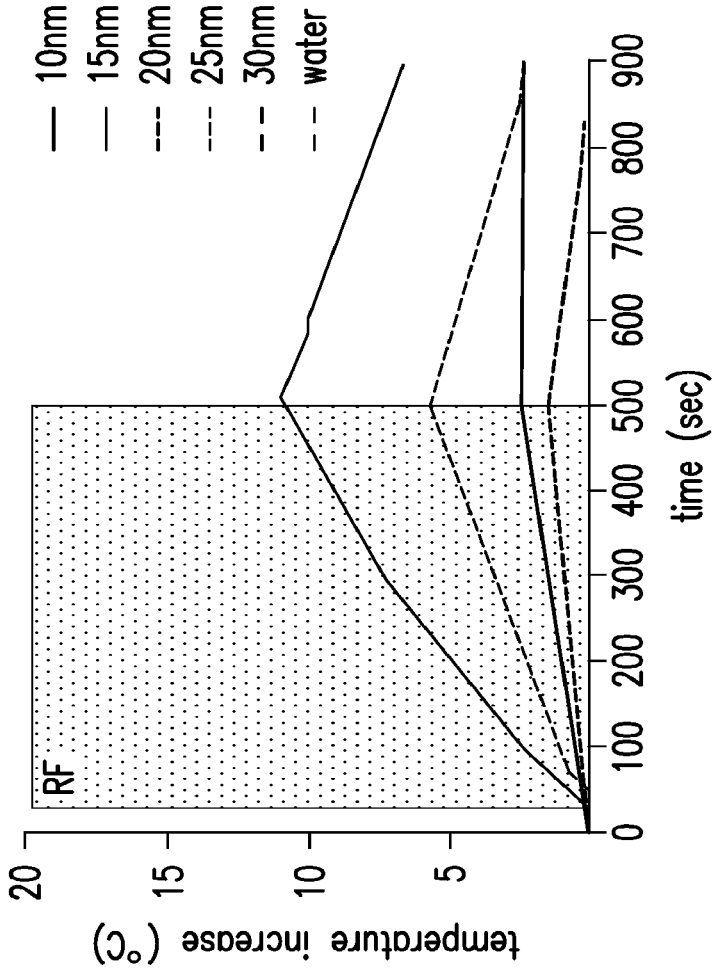

10nm
15nm
20nm
25nm
30nm
water
RF
temperature increase (°C)
20
15
10
5
0
100
200
300
400
500
600
700
800
900
time (sec)

FIG. 2E

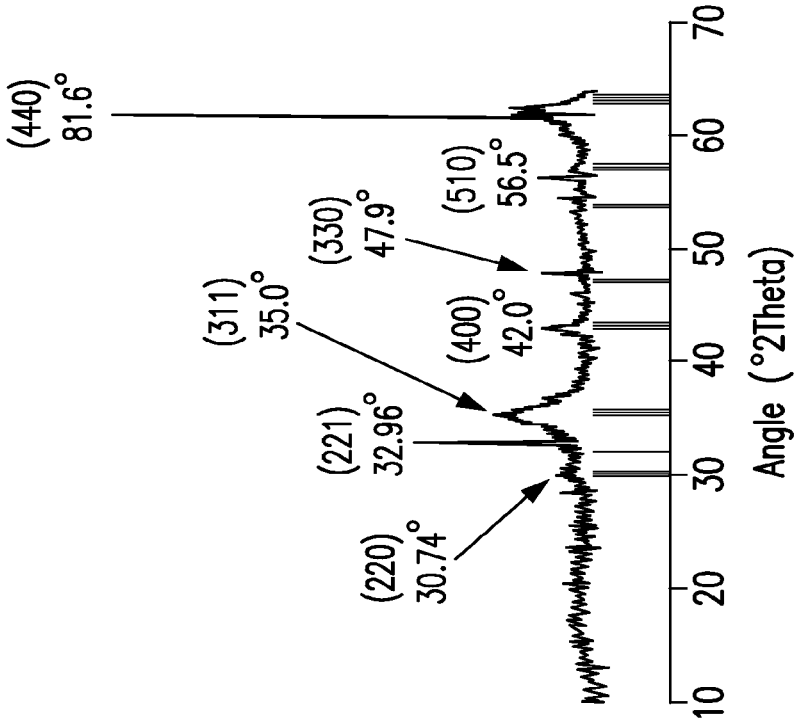

(440)
81.6°
(330)
47.9°
(510)
56.5°
(311)
35.0°
(400)
42.0°
(221)
32.96°
(220)
30.74°
10
20
30
40
50
60
70
Angle (°2Theta)

FIG. 2D

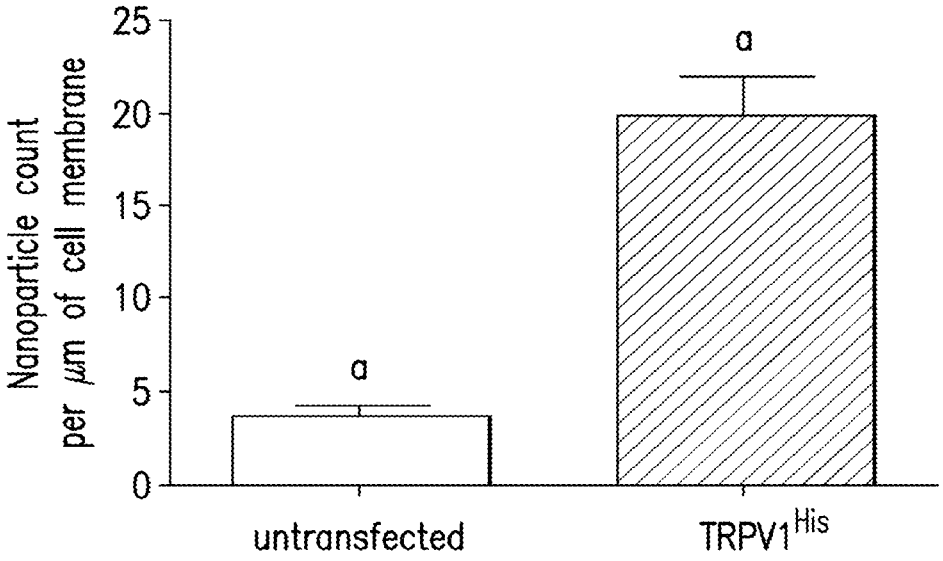

Nanoparticle count
per μm of cell membrane
25
20
15
10
5
0
a
a
untransfected
TRPV1His

FIG. 3A

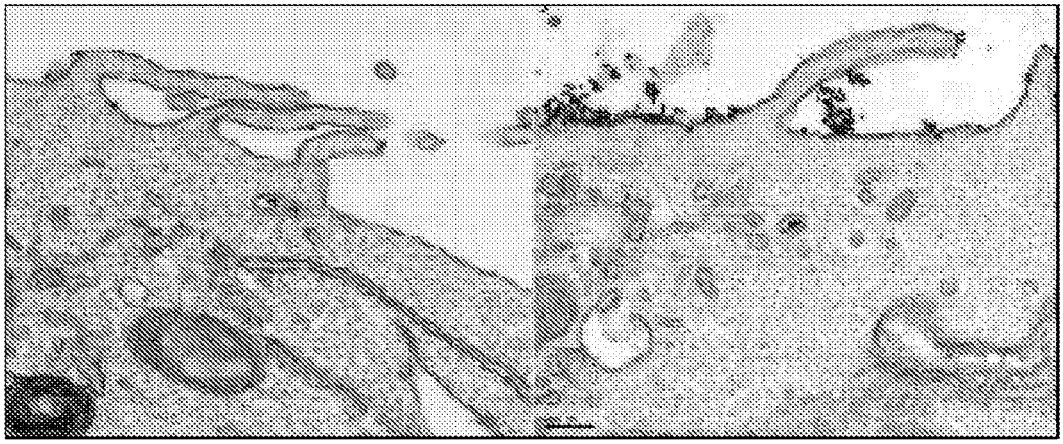


FIG. 3B

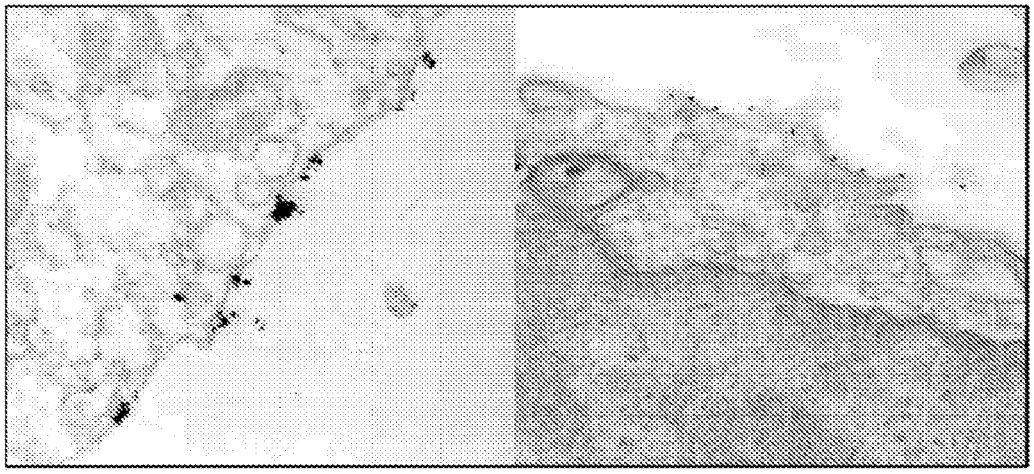


FIG. 3C

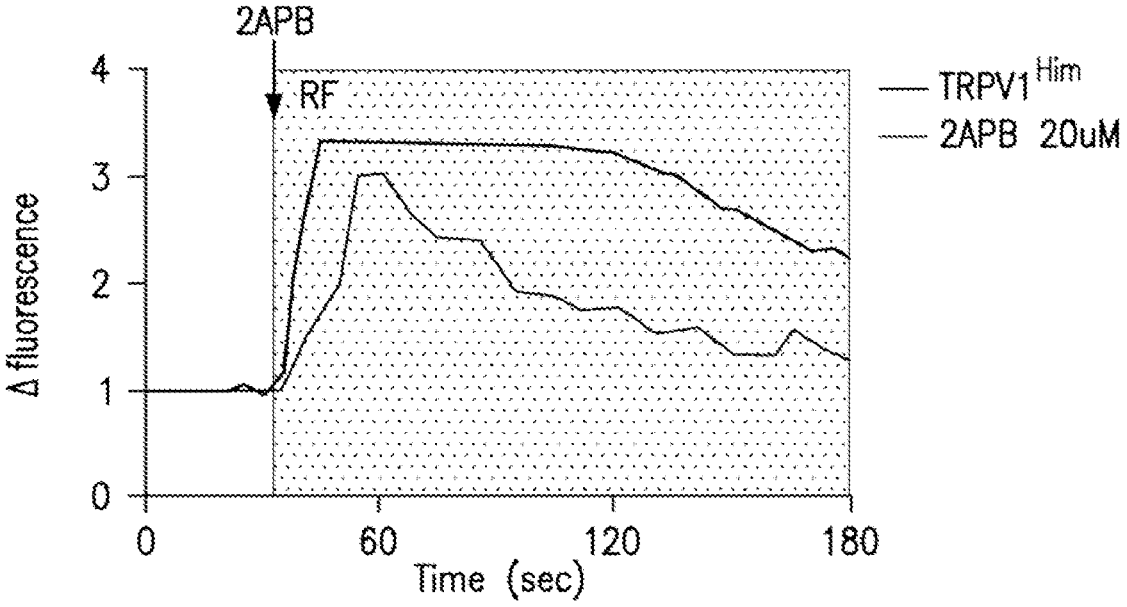

2APB
RF
TRPV1 Hm
2APB 20uM
Δ fluorescence
0
1
2
3
4
0
60
120
180
Time (sec)

FIG. 3D

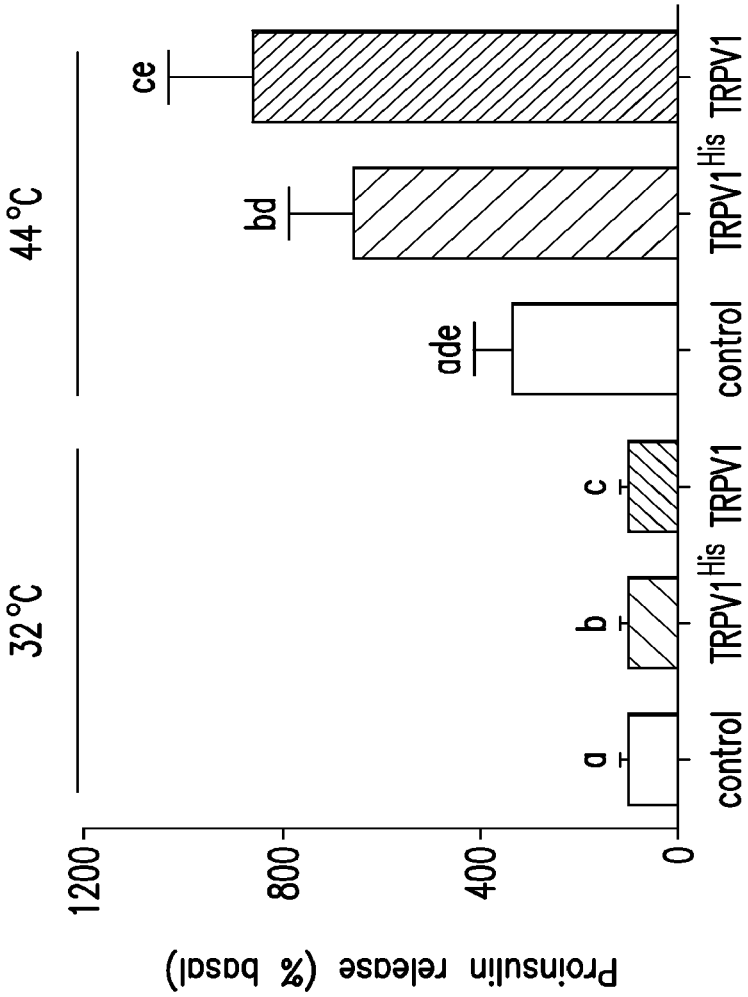

Proinsulin release (% basal)
1200
800
400
0
32 °C
44 °C
a
b
c
ade
bd
ce
control
TRPV1His
TRPV1
control
TRPV1His
TRPV1

FIG. 4

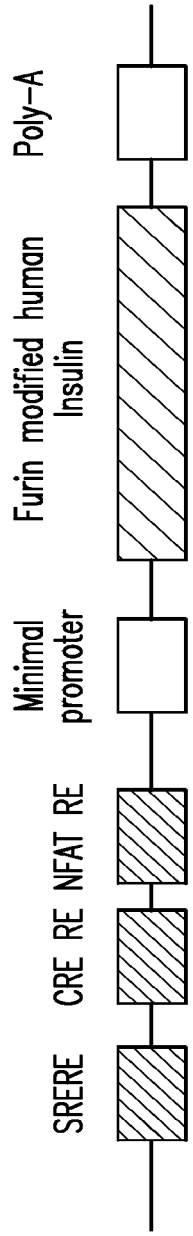


FIG. 5A

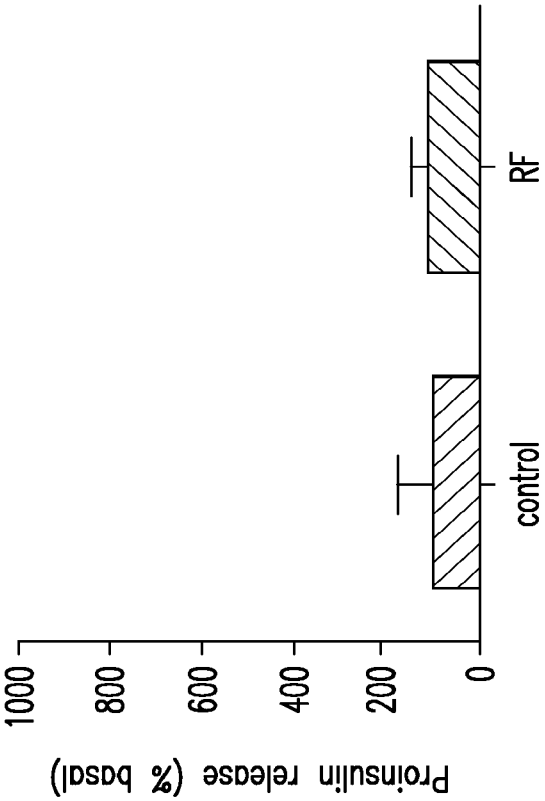


FIG. 5C

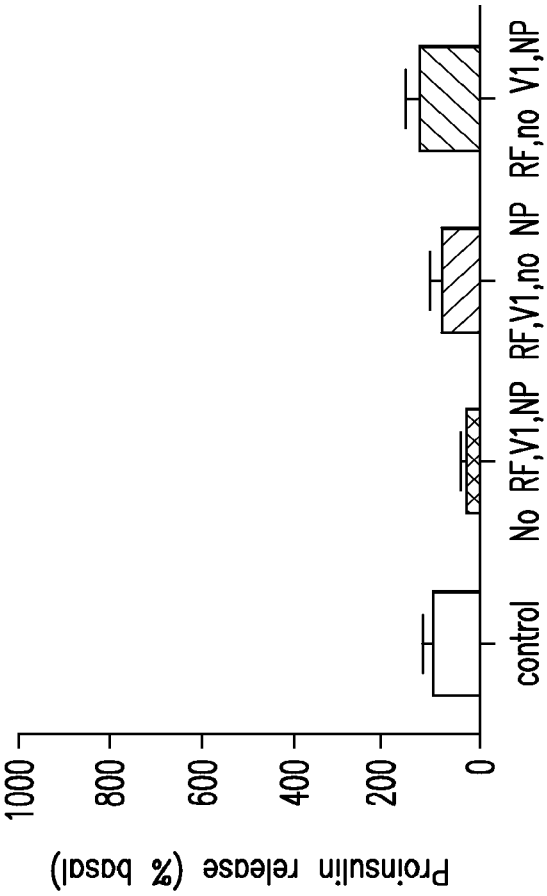


FIG. 5B

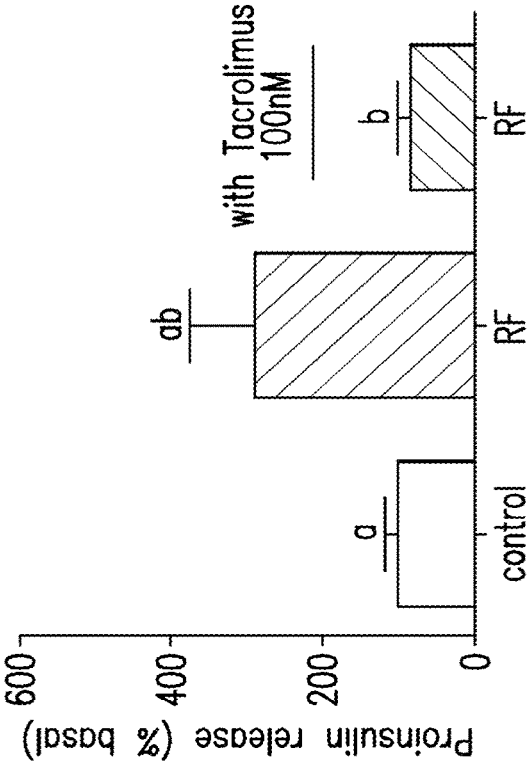

Proinsulin release (% basal)
600
400
200
0
a
ab
b
control
RF
RF
with Tacrolimus
100nM

FIG. 5E

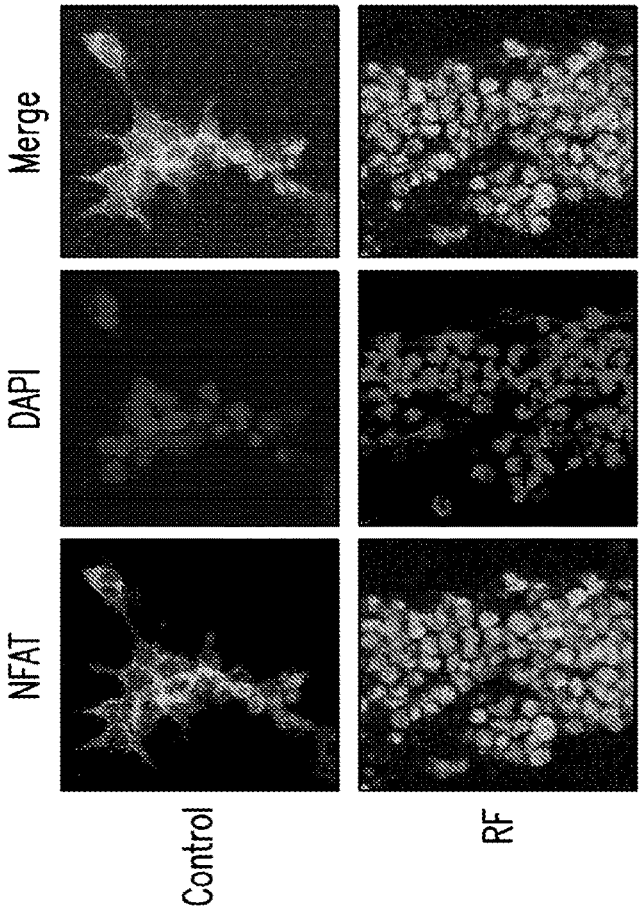

NFAT
DAPI
Merge
Control
RF

FIG. 5D

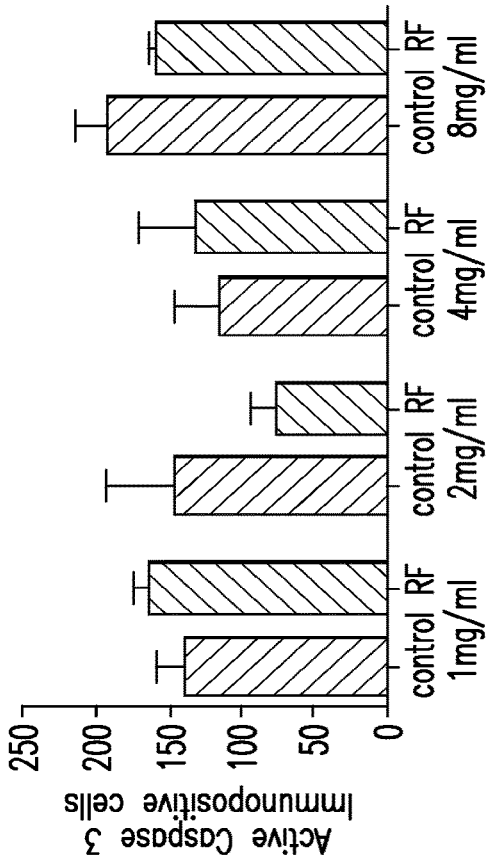

Active Caspase 3
immunopositive cells
250
200
150
100
50
0
control
RF
1mg/ml
control
RF
2mg/ml
control
RF
4mg/ml
control
RF
8mg/ml

FIG. 5G

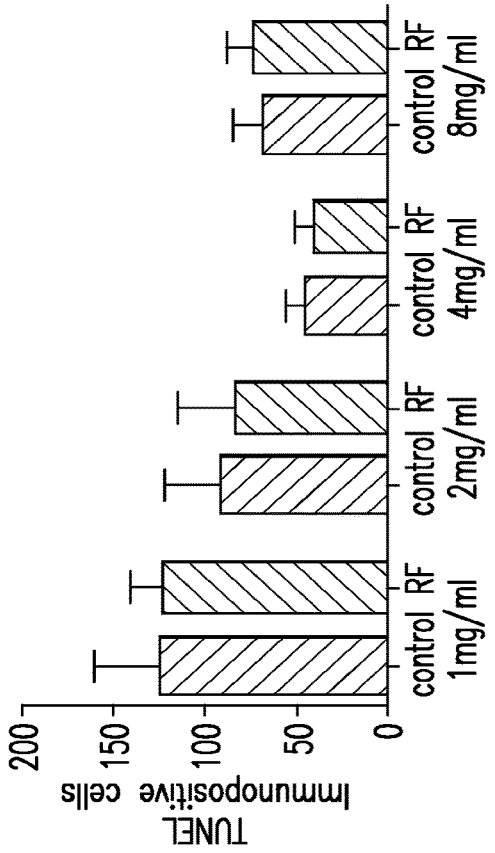

TUNEL
immunopositive cells
200
150
100
50
0
control
RF
1mg/ml
control
RF
2mg/ml
control
RF
4mg/ml
control
RF
8mg/ml

FIG. 5F

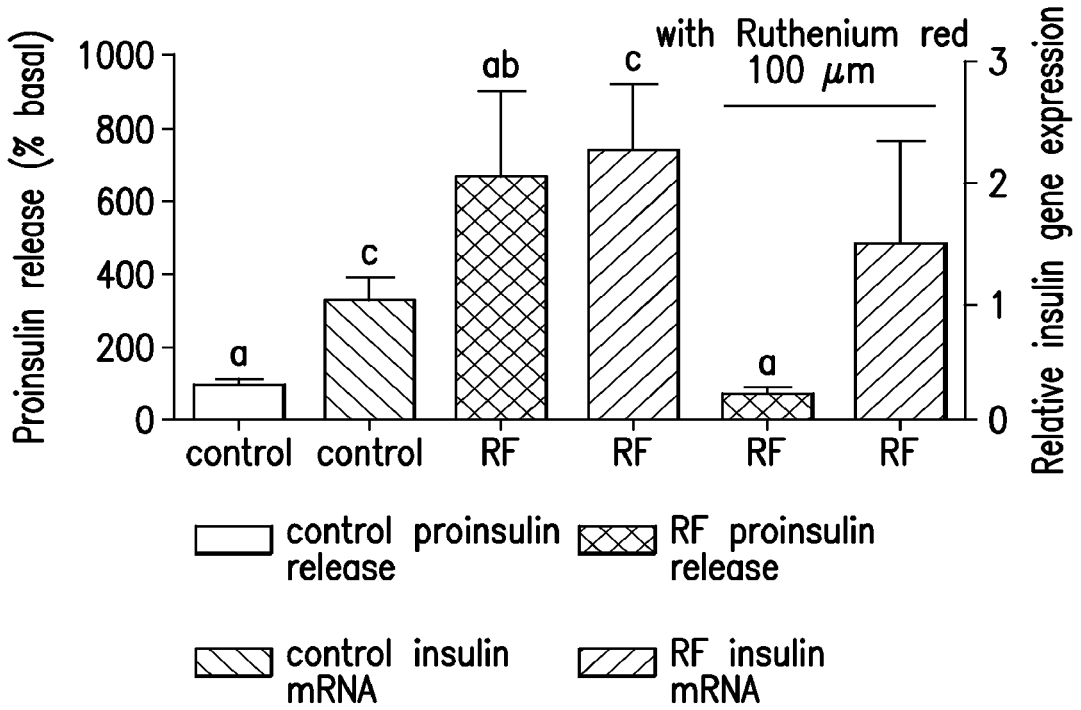

Proinsulin release (% basal)
1000
800
600
400
200
0
a
c
ab
c
a
with Ruthenium red
100 μm
3
2
1
0
Relative insulin gene expression
control
control
RF
RF
RF
RF
control proinsulin release
RF proinsulin release
control insulin mRNA
RF insulin mRNA

FIG. 6A

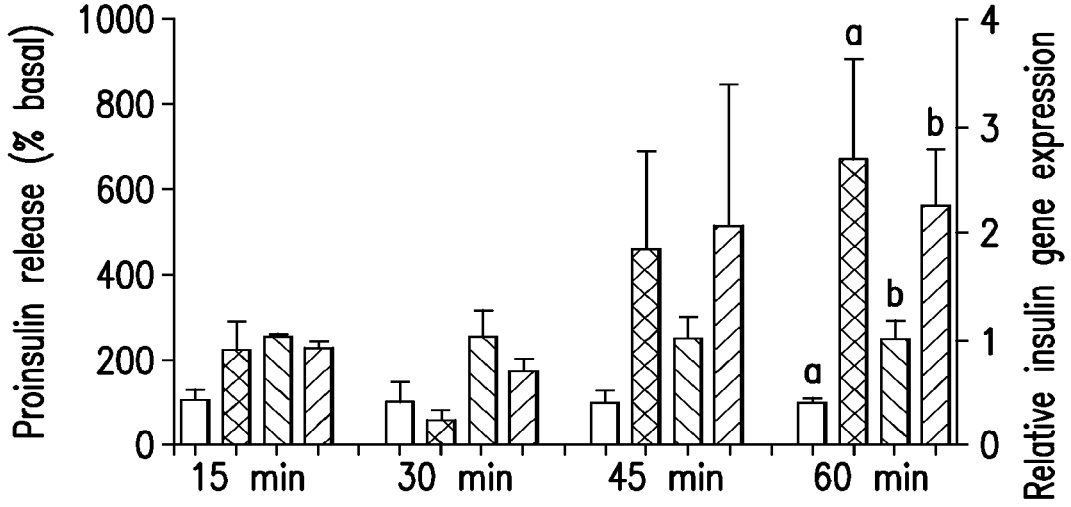

Proinsulin release (% basal)
1000
800
600
400
200
0
a
a
b
b
4
3
2
1
0
Relative insulin gene expression
15 min
30 min
45 min
60 min

FIG. 6B

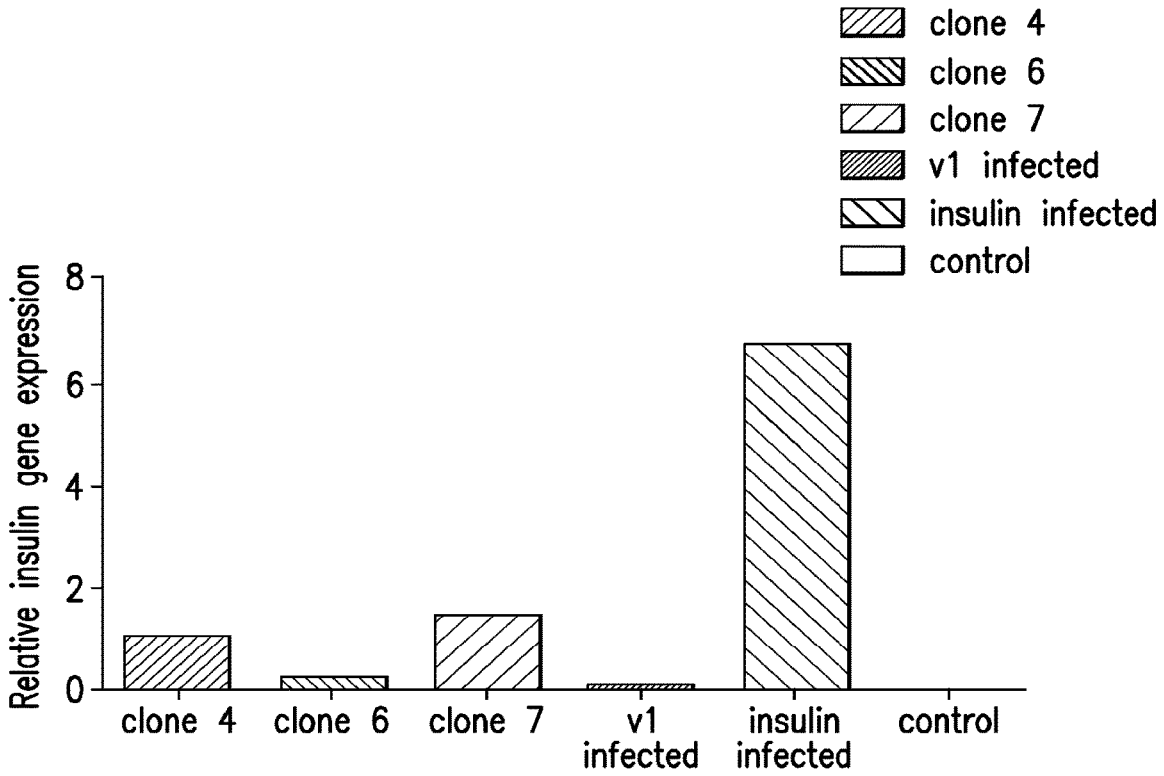

clone 4
clone 6
clone 7
v1 infected
insulin infected
control
Relative insulin gene expression
8
6
4
2
0
clone 4
clone 6
clone 7
v1 infected
insulin infected
control

FIG. 7A

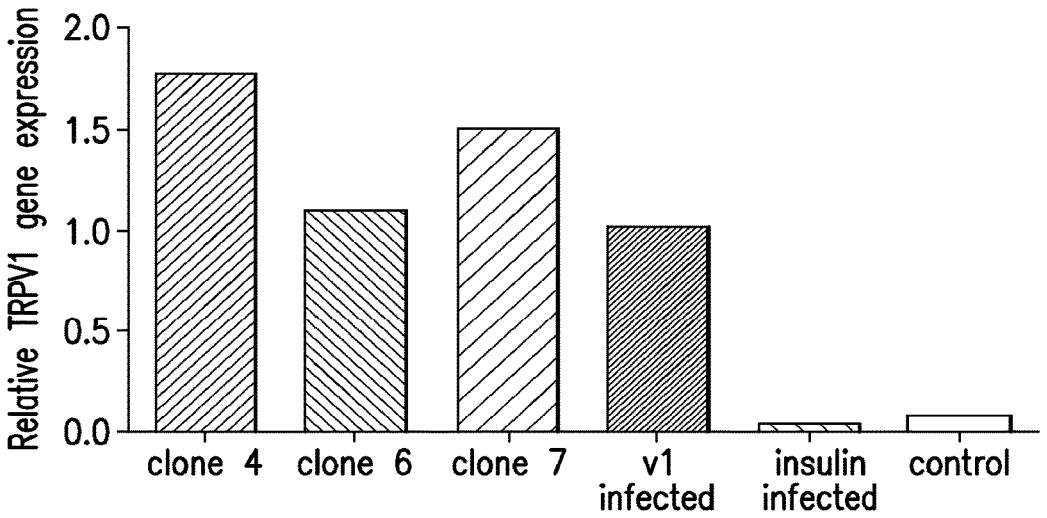

Relative TRPV1 gene expression
2.0
1.5
1.0
0.5
0.0
clone 4
clone 6
clone 7
v1 infected
insulin infected
control

FIG. 7B

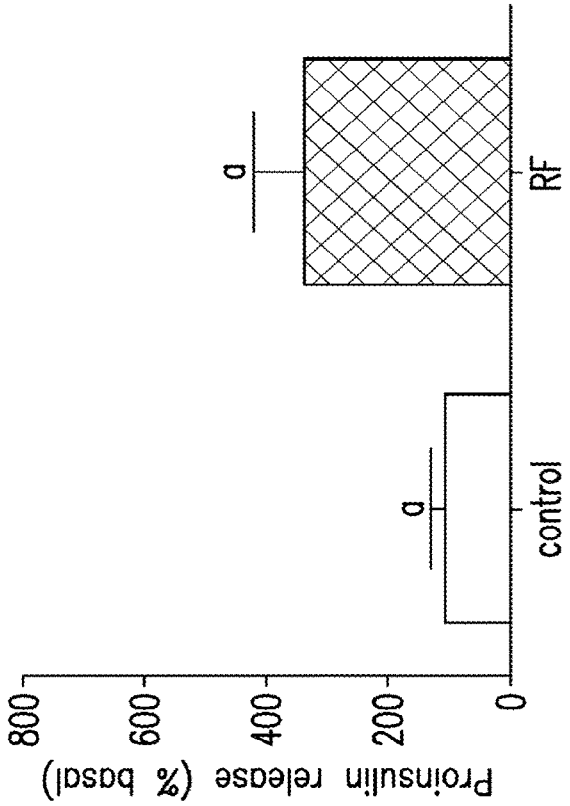

Proinsulin release (% basal)
800
600
400
200
0
a
a
control
RF

FIG. 7D

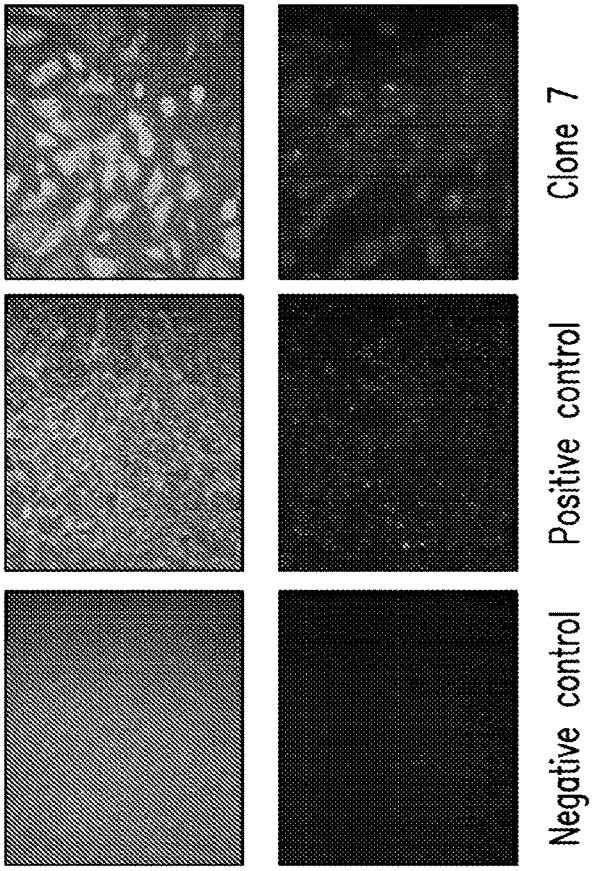

Negative control
Positive control
Clone 7

FIG. 7C

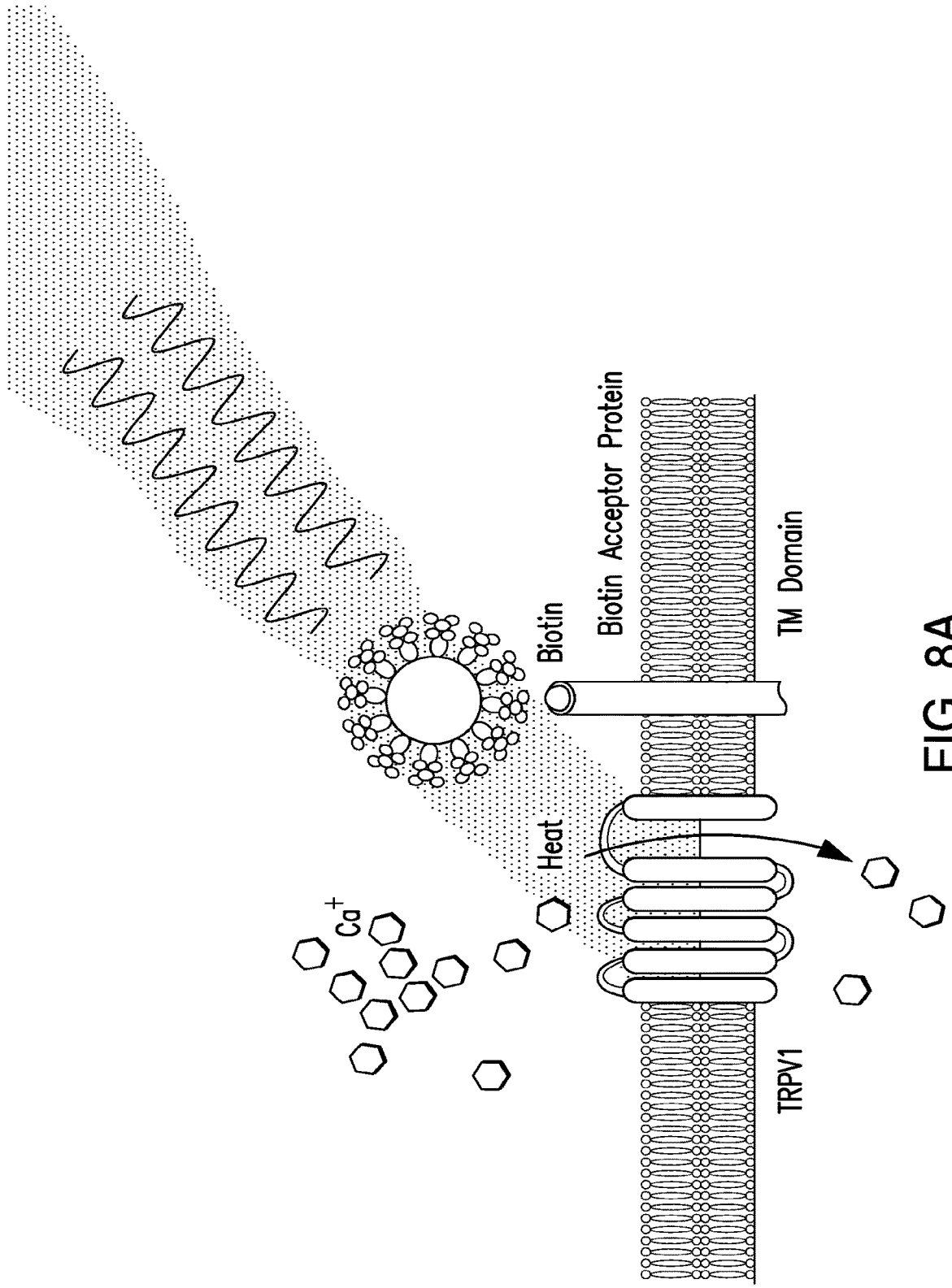


FIG. 8A

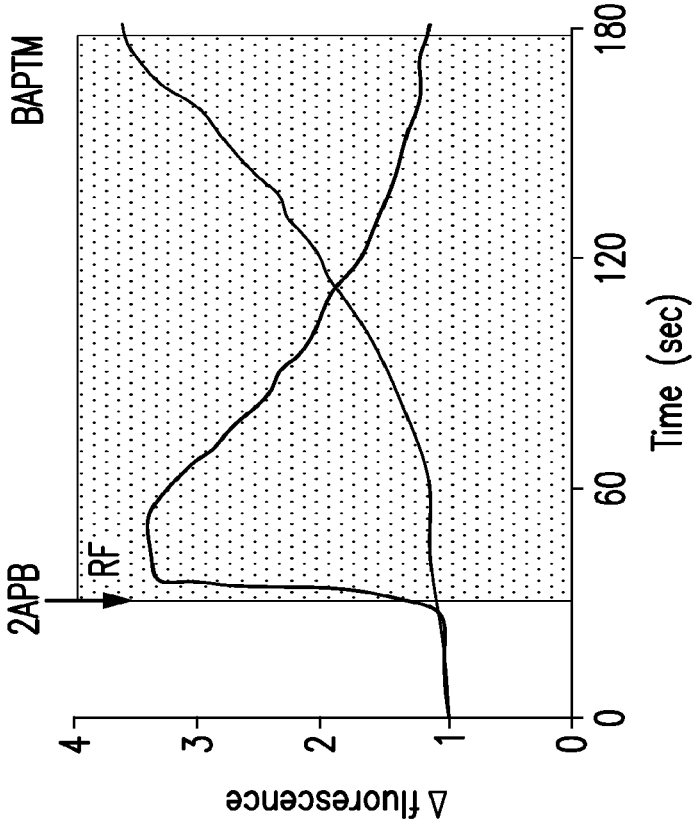

2APB
TRPV1
BAPTM
2APB
RF
Δ fluorescence
0
1
2
3
4
0
60
120
180
Time (sec)

FIG. 8C

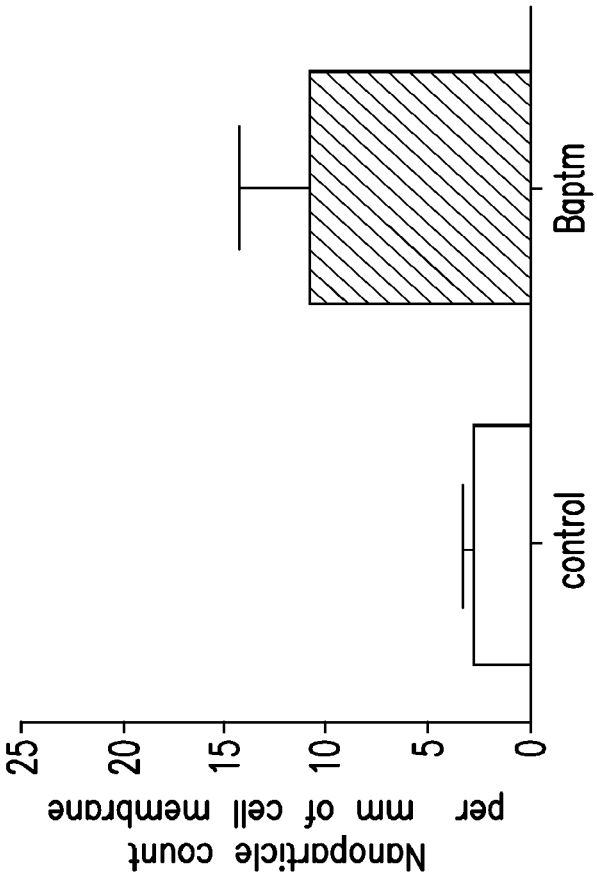

Nanoparticle count per mm of cell membrane
0
5
10
15
20
25
control
Baptm

FIG. 8B

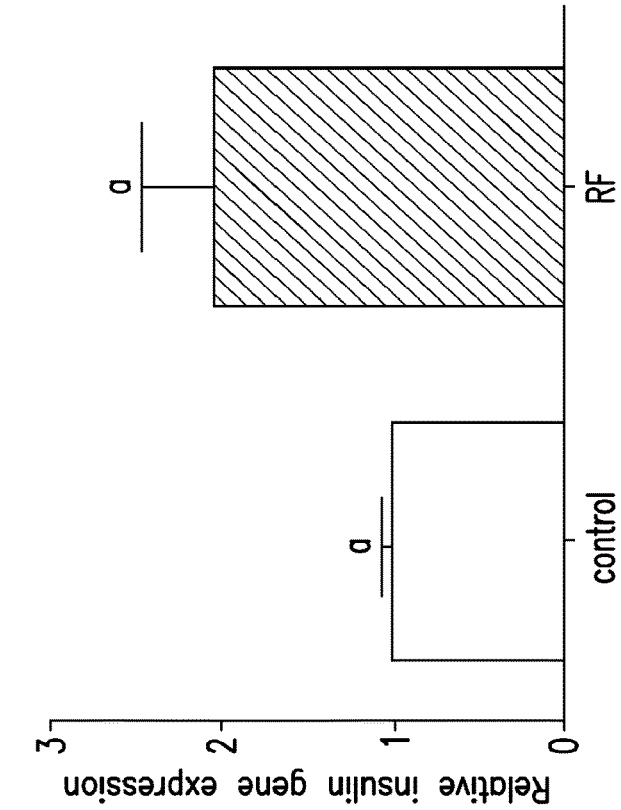

Relative insulin gene expression
3
2
1
0
a
a
control
RF

FIG. 8E

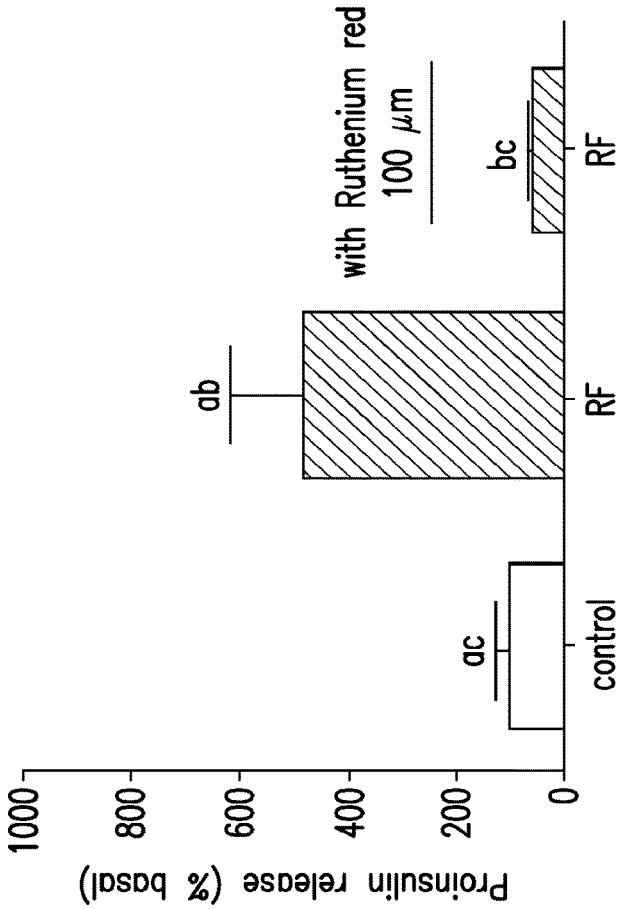

Proinsulin release (% basal)
1000
800
600
400
200
0
ac
ab
with Ruthenium red
100 μm
bc
control
RF
RF

FIG. 8D

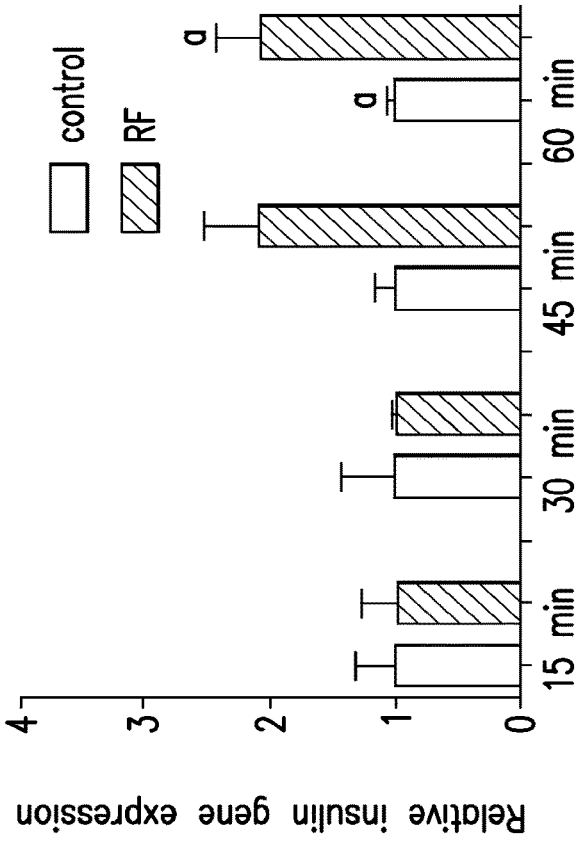

Relative insulin gene expression
0
1
2
3
4
15 min
30 min
45 min
60 min
a
a
control
RF

FIG. 8G

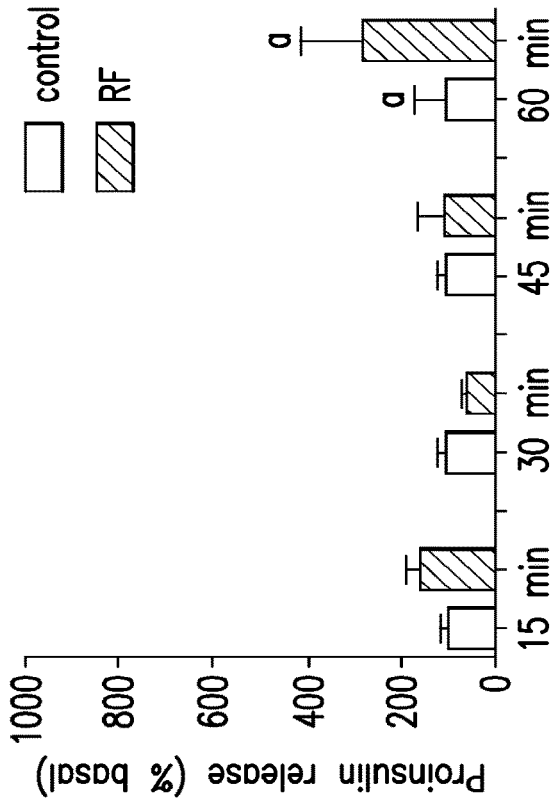

Proinsulin release (% basal)
0
200
400
600
800
1000
15 min
30 min
45 min
60 min
a
a
control
RF

FIG. 8F

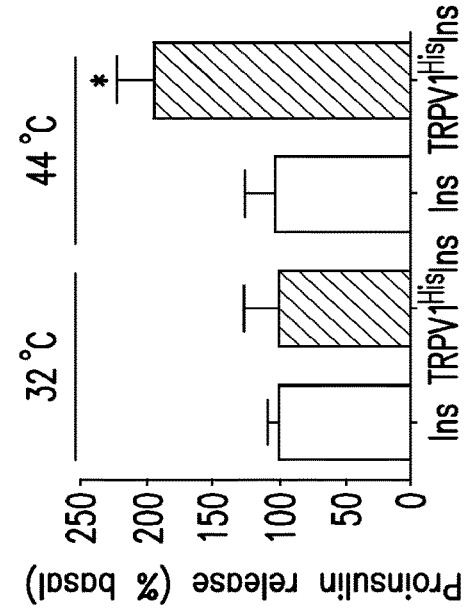


FIG. 9A

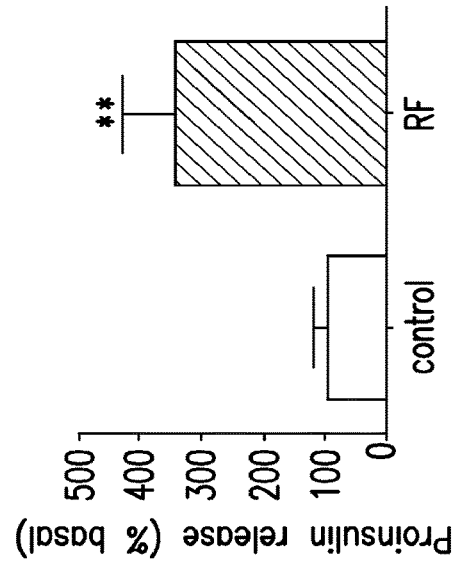


FIG. 9B

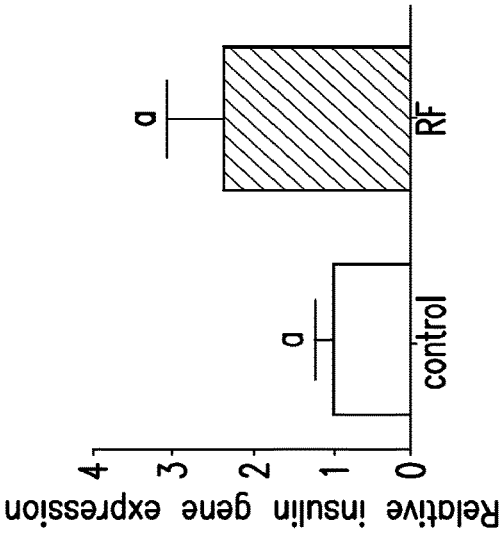


FIG. 9C

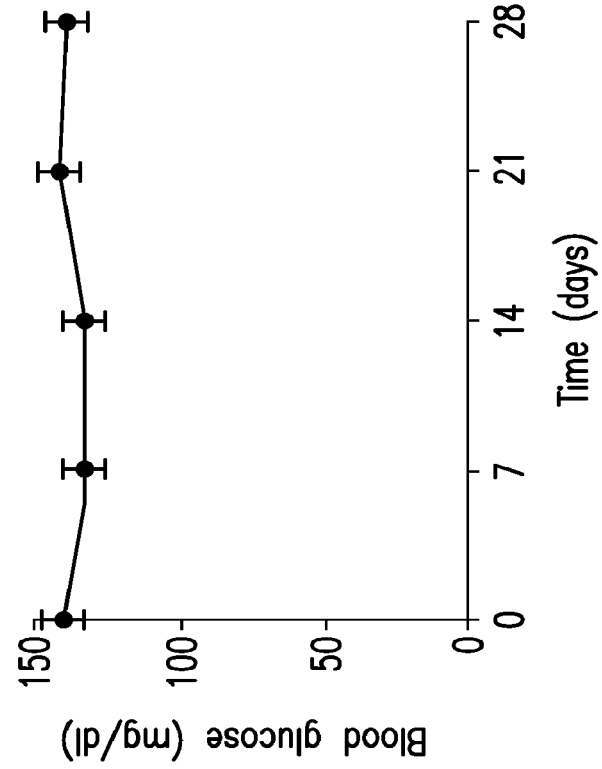

Blood glucose (mg/dl)
150
100
50
0
0
7
14
21
28
Time (days)

FIG. 9E

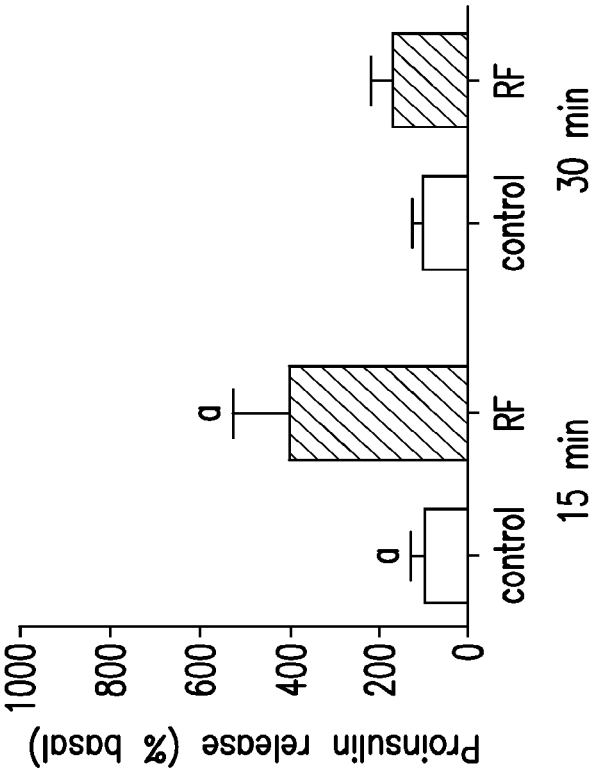

Proinsulin release (% basal)
1000
800
600
400
200
0
a
a
control
RF
control
RF
15 min
30 min

FIG. 9D

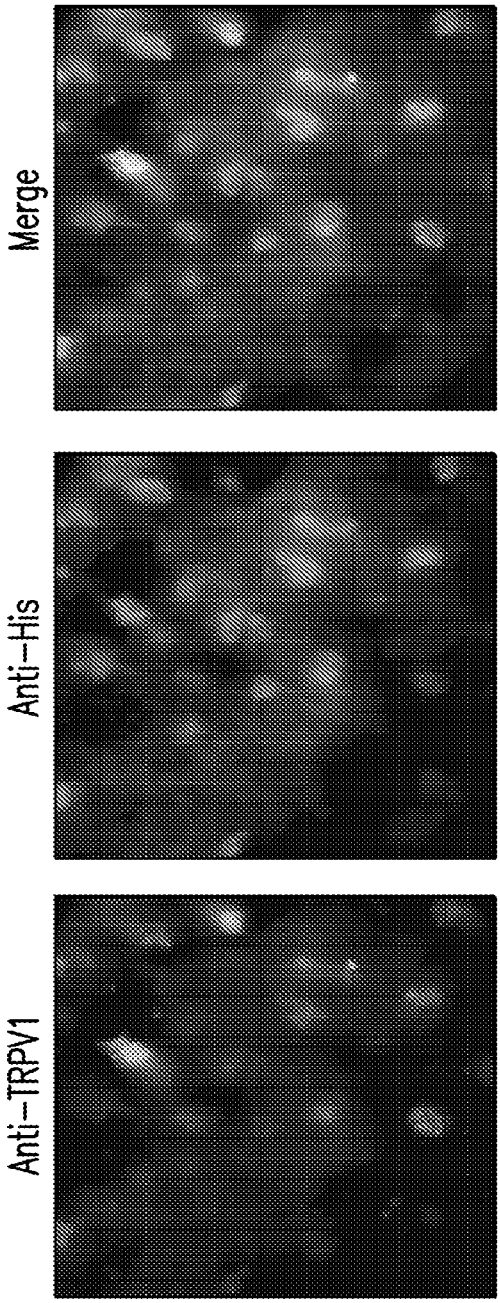


FIG. 9F

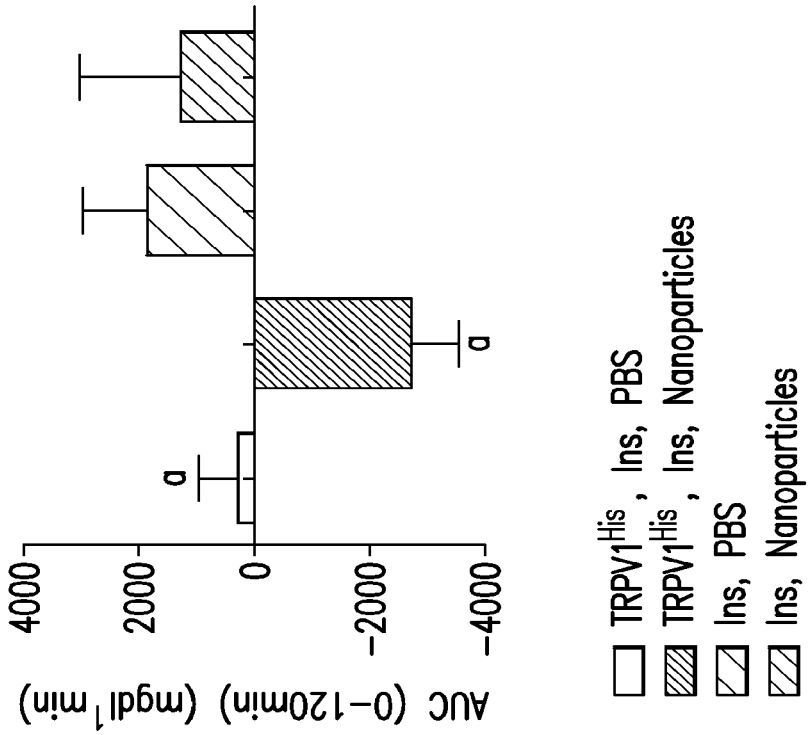


FIG. 10B

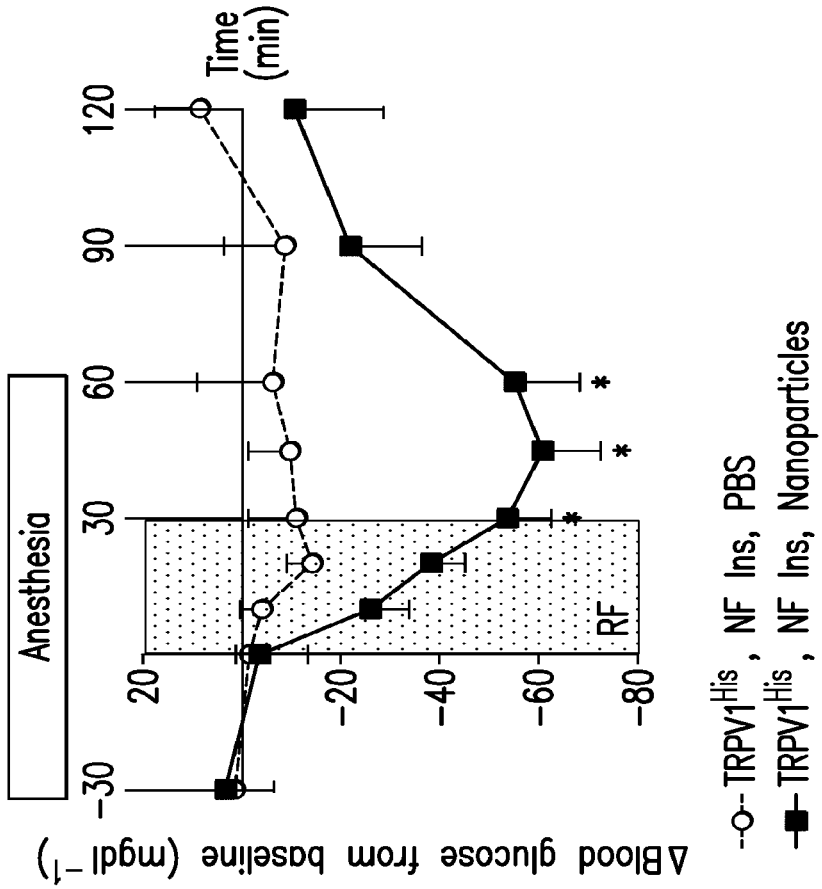


FIG. 10A

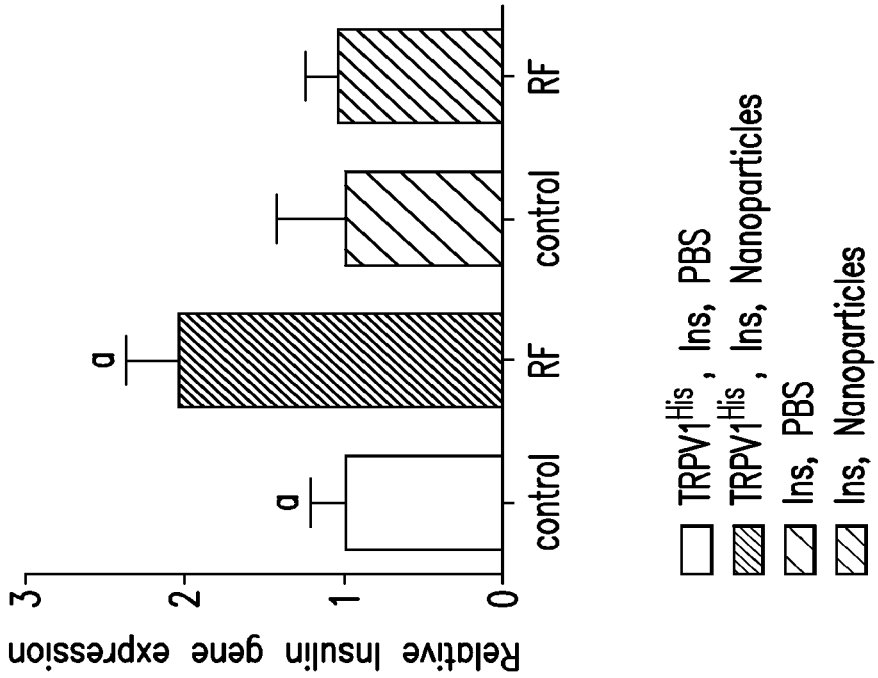


FIG. 10D

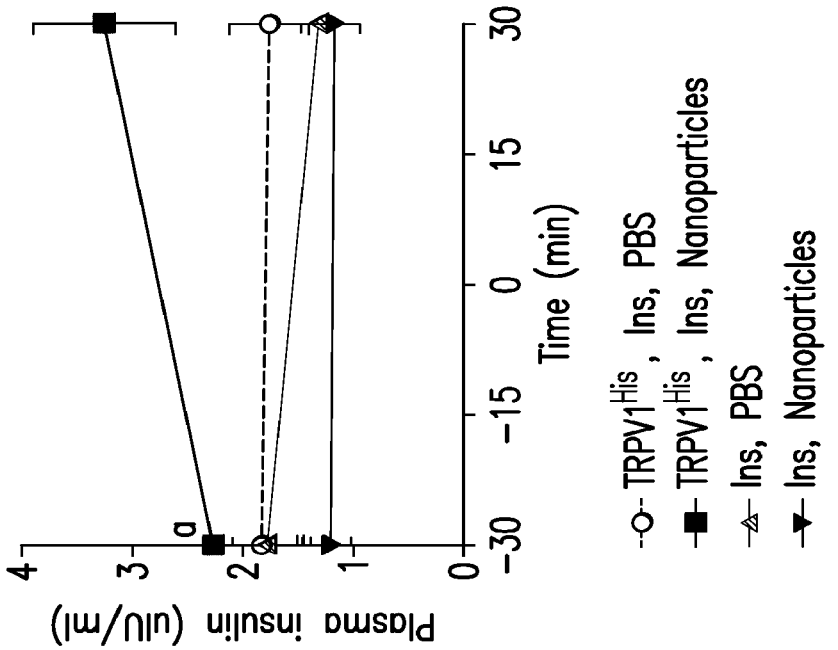


FIG. 10C

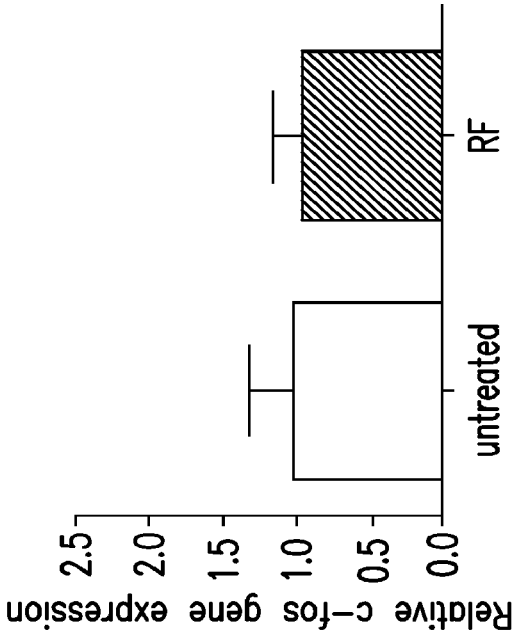


FIG. 11B

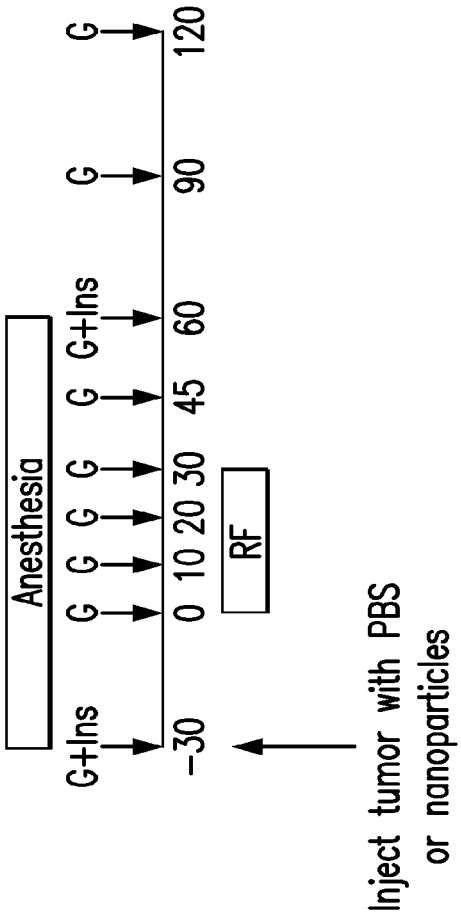


FIG. 11A

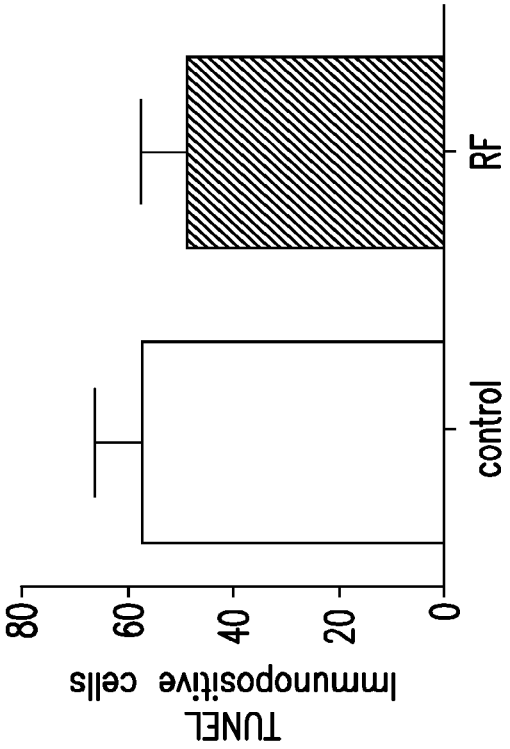


FIG. 11C

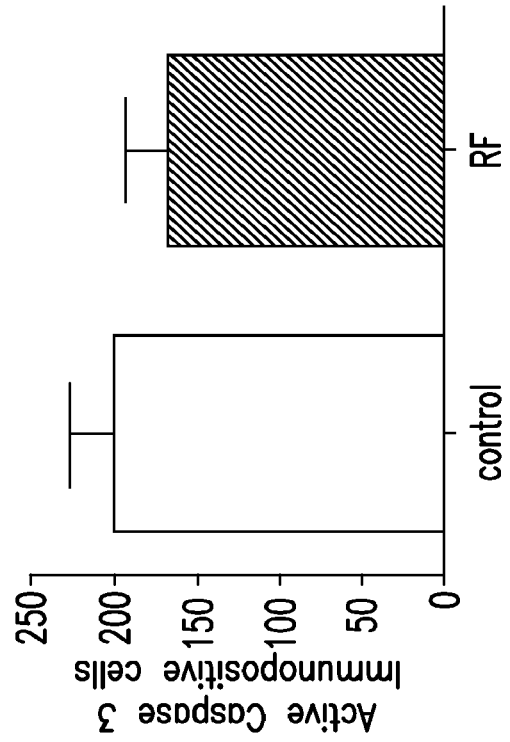


FIG. 11D

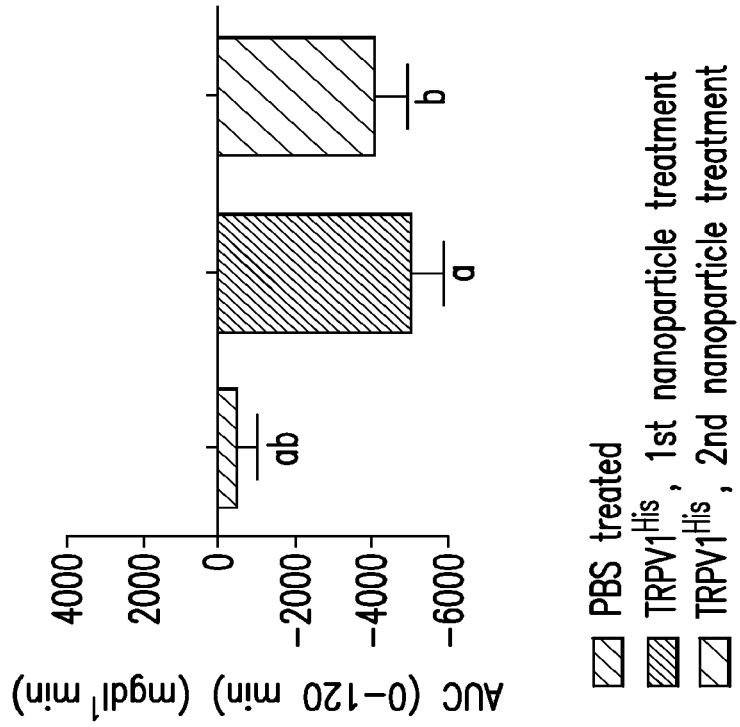


FIG. 11F

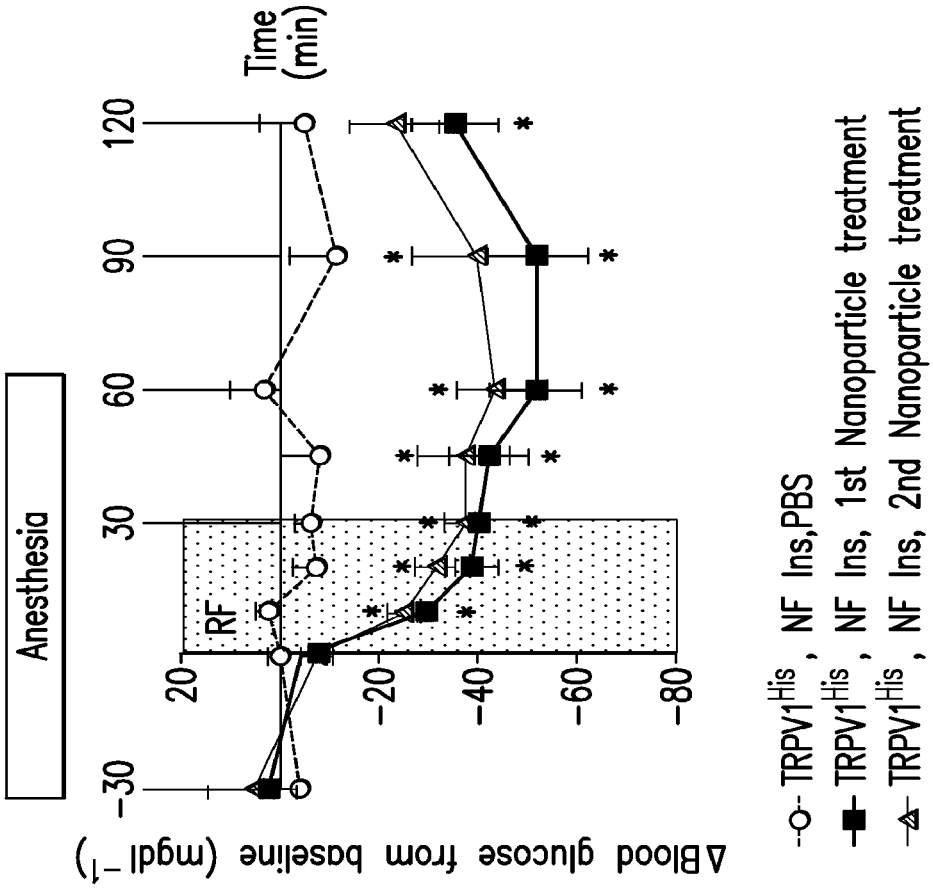


FIG. 11E

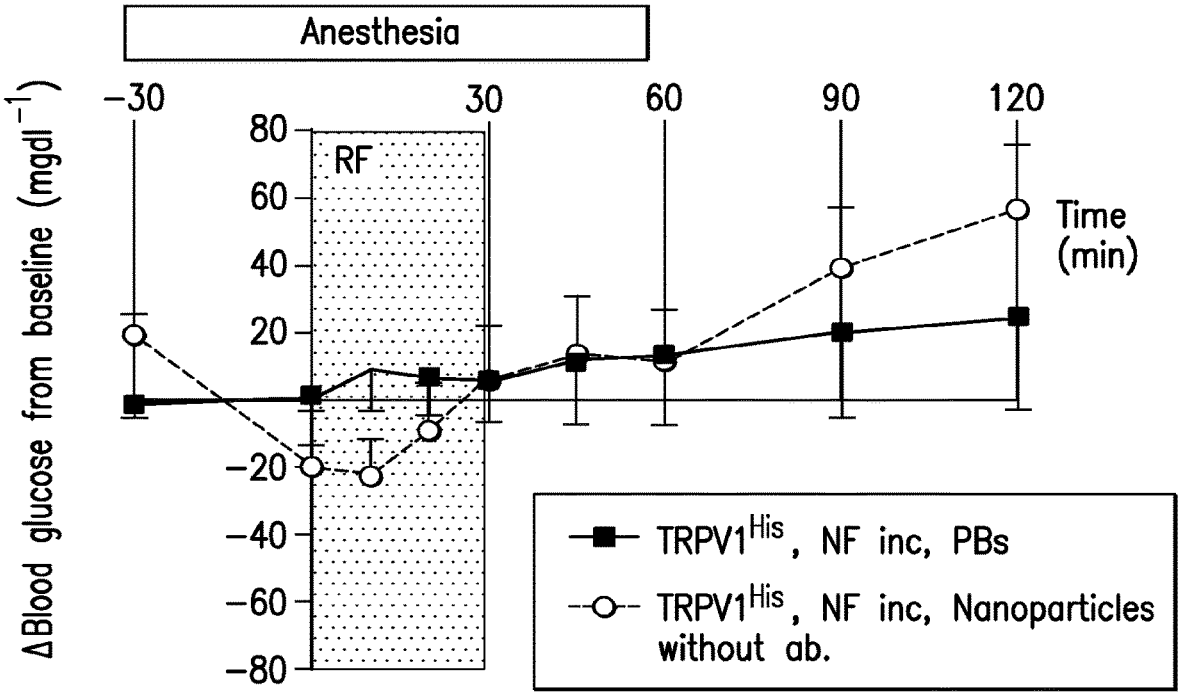


FIG. 12A

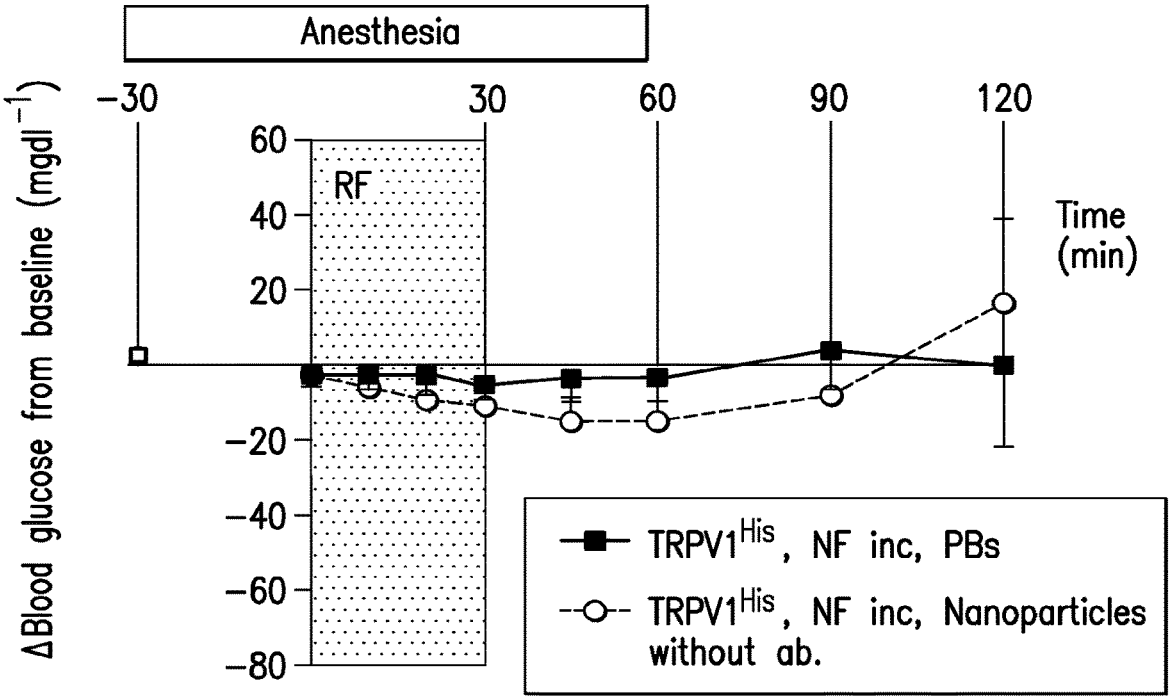


FIG. 12B

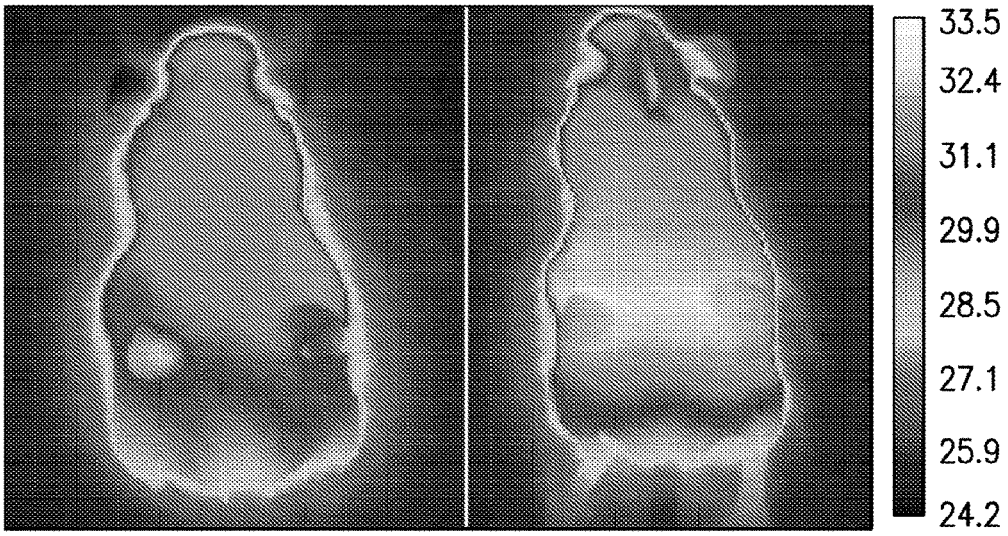


FIG. 12C

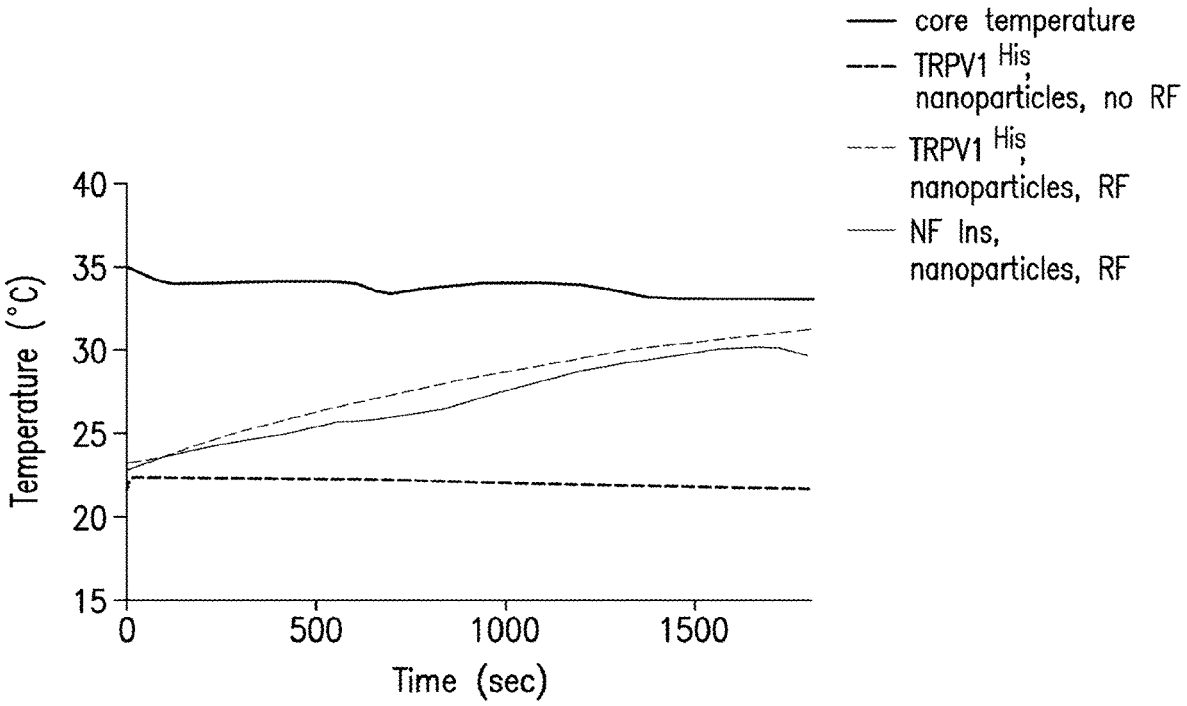


FIG. 12D

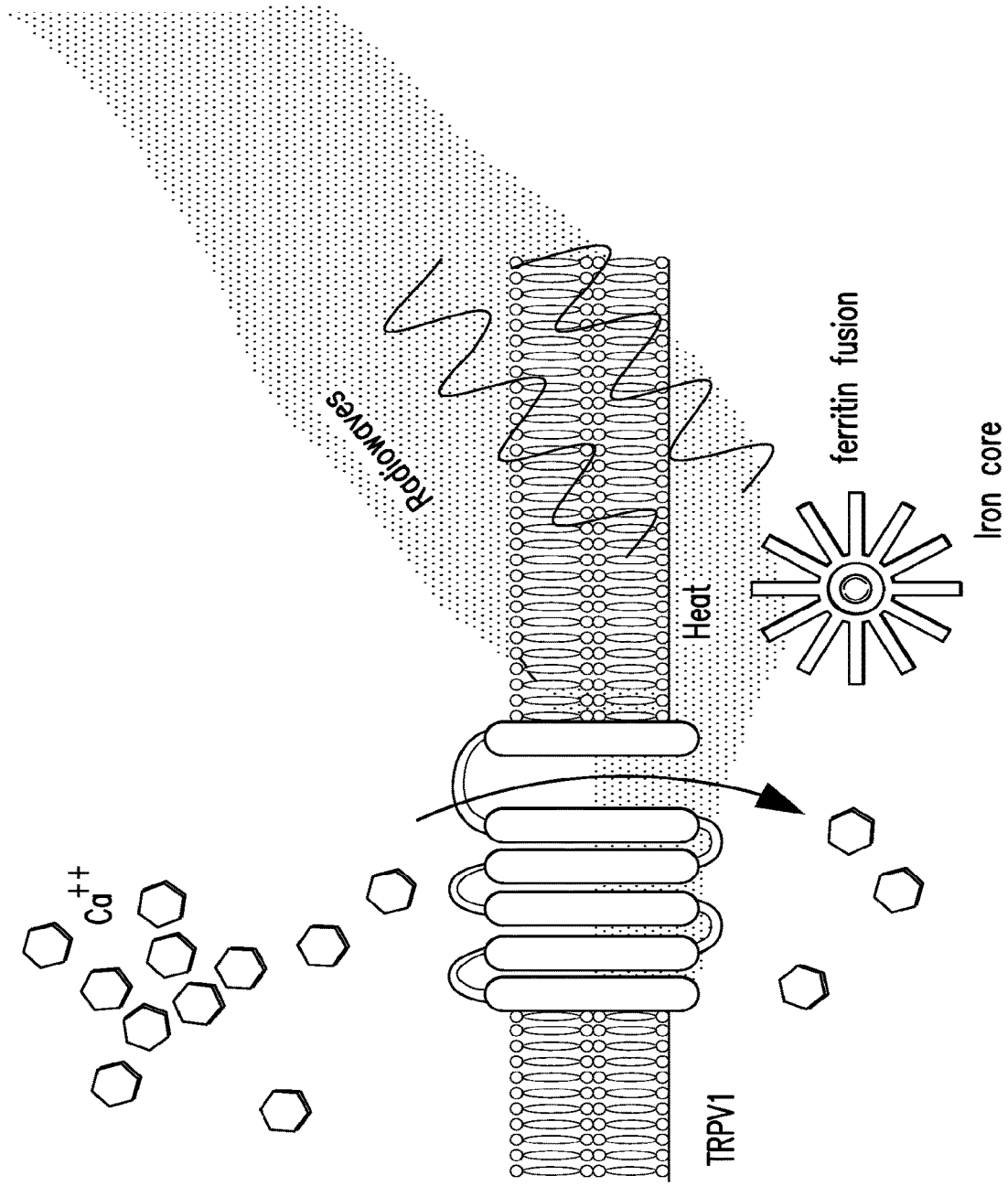


FIG. 13A

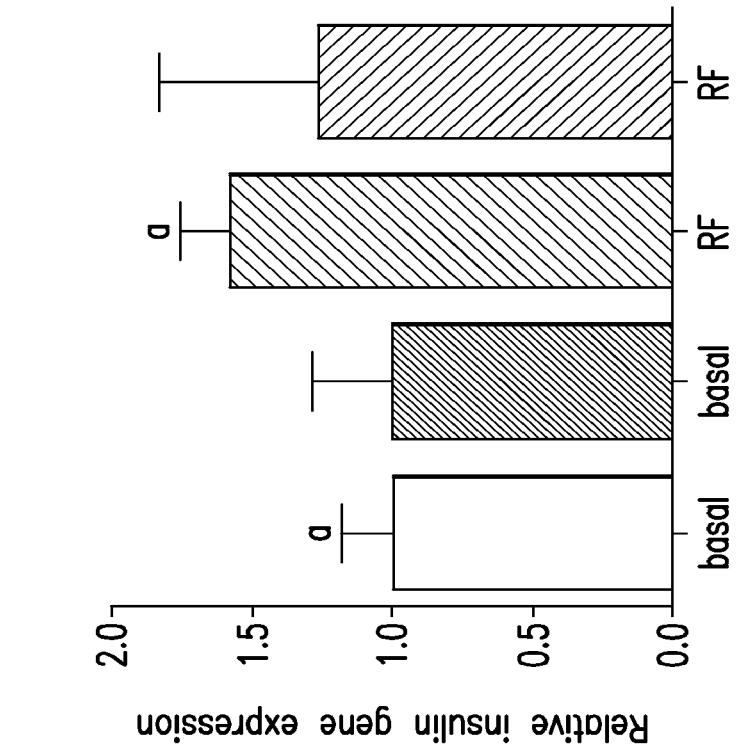


FIG. 13C

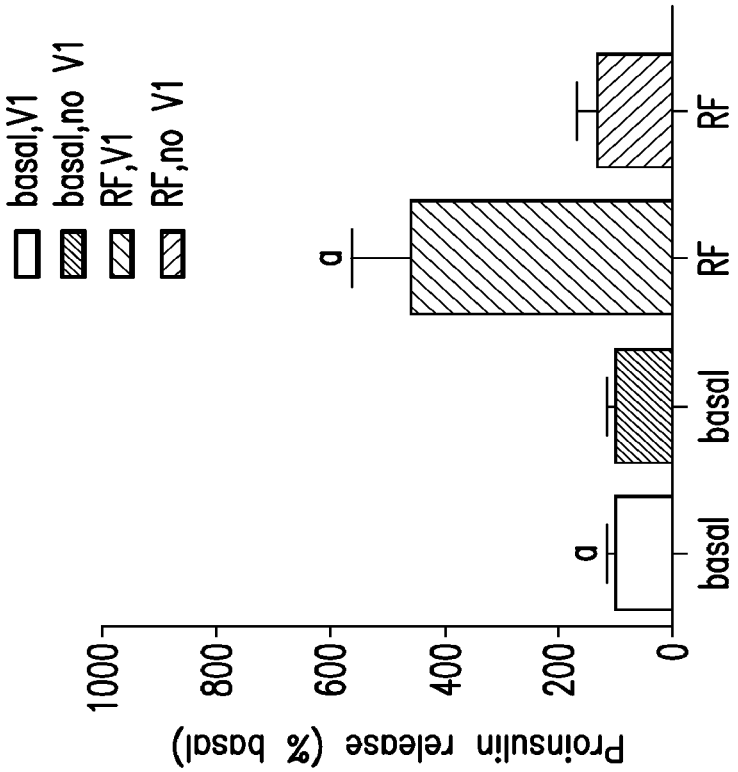


FIG. 13B

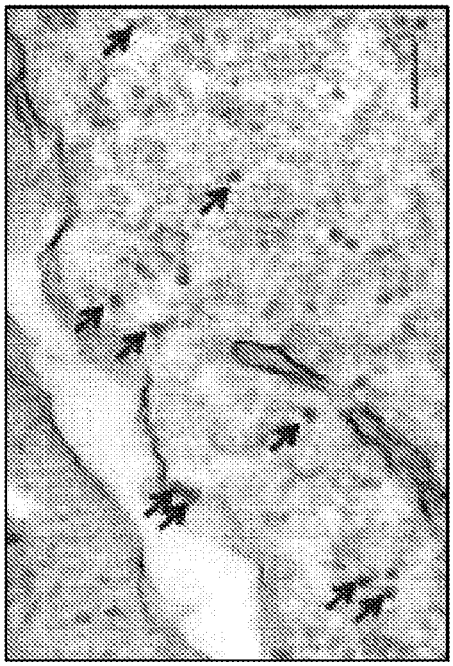


FIG. 14B

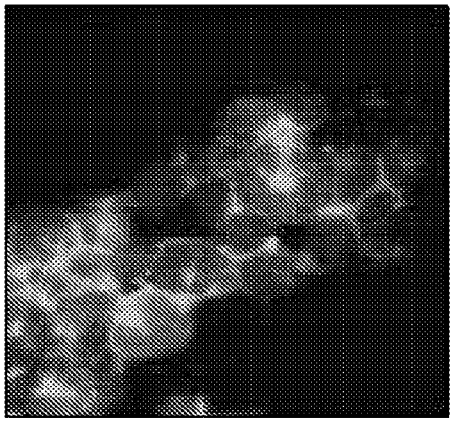


FIG. 14A

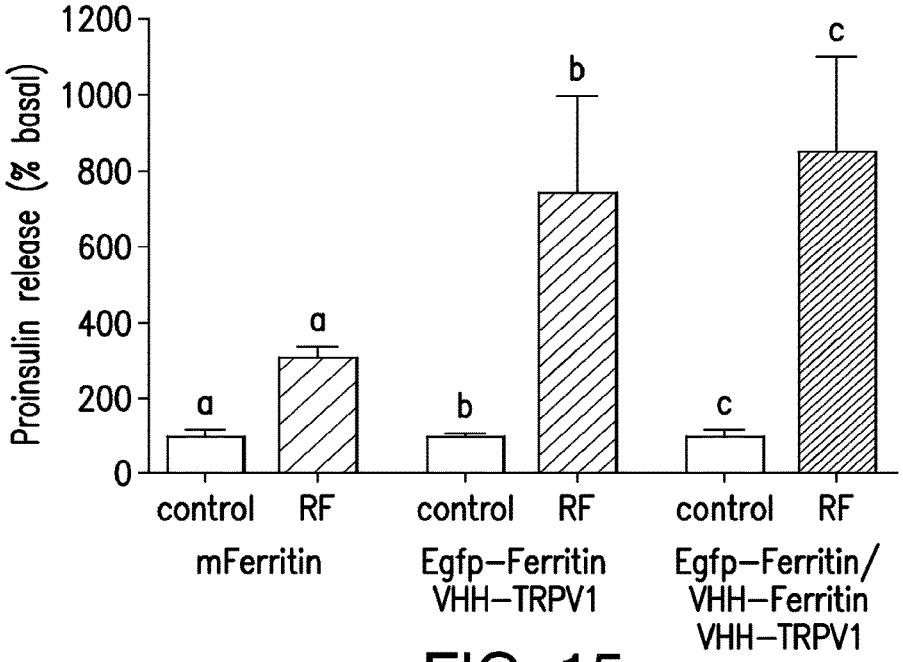


FIG. 15

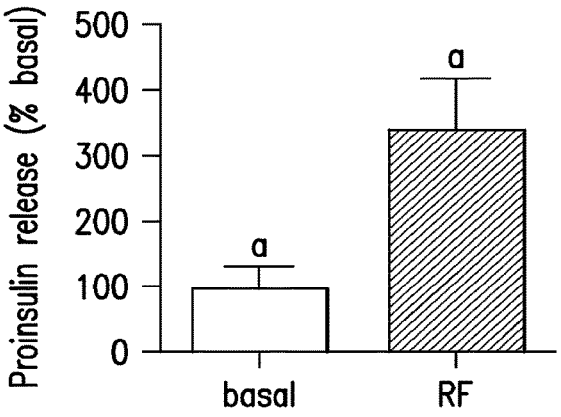


FIG. 16A

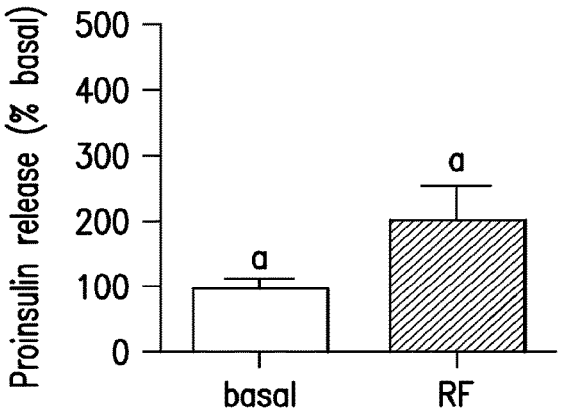


FIG. 16B

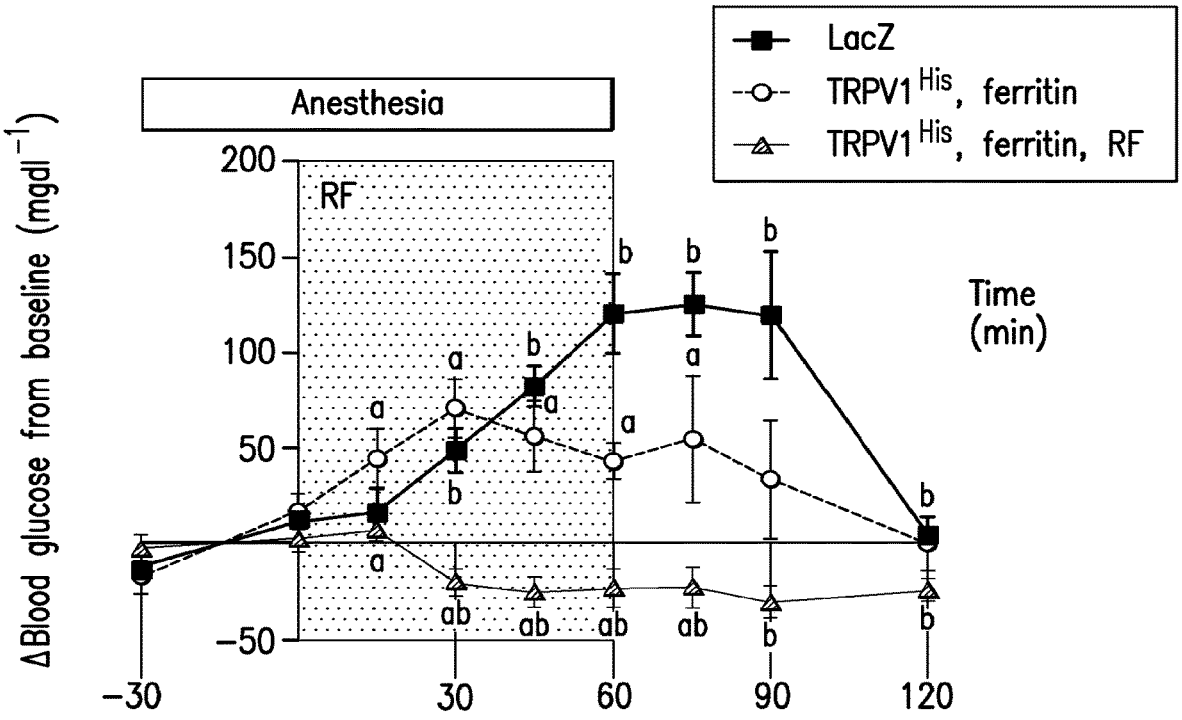


FIG. 17

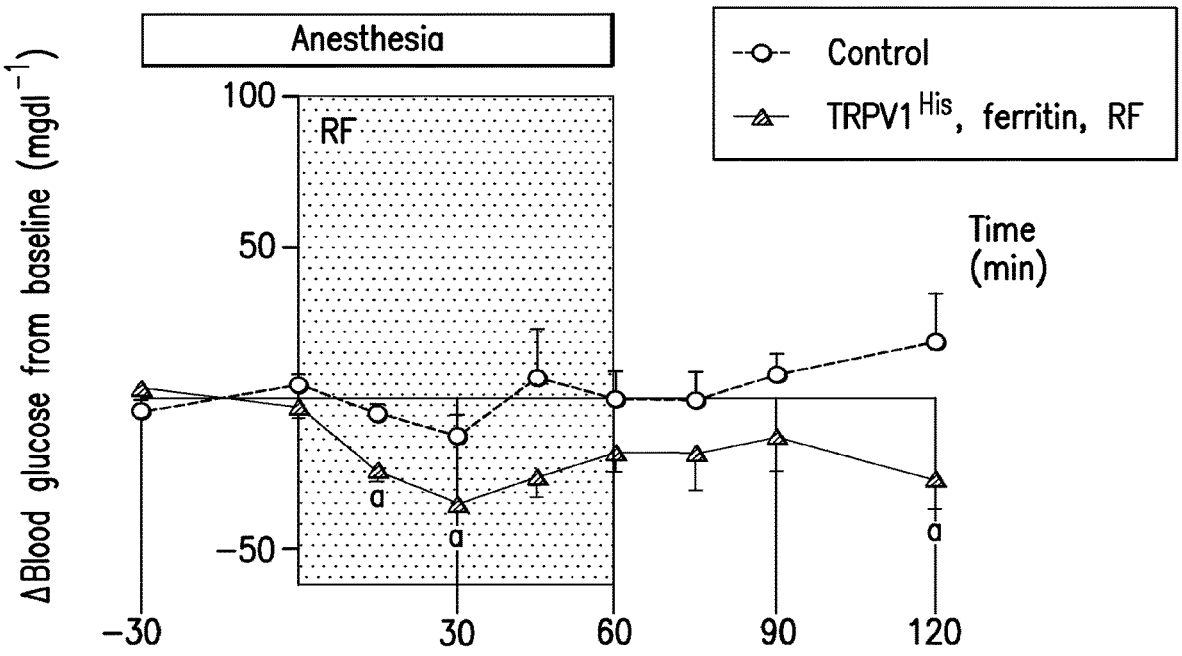


FIG. 18A

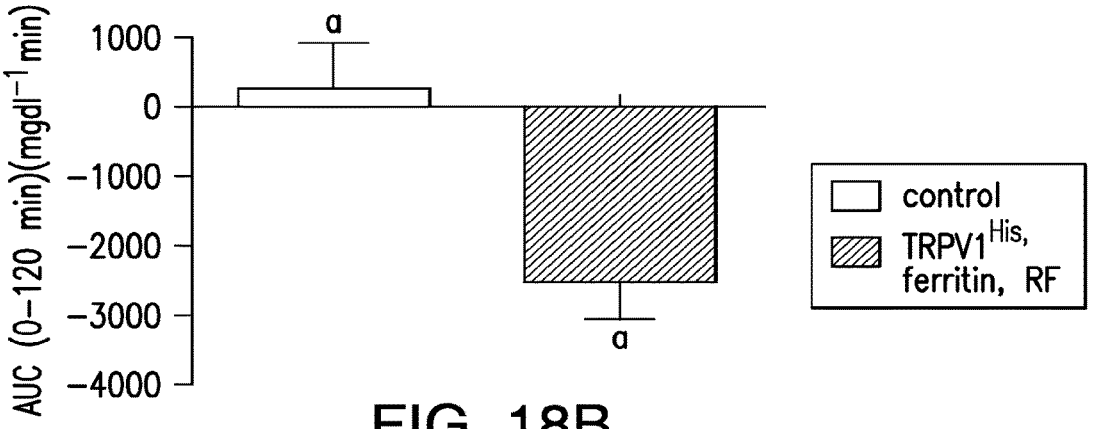


FIG. 18B

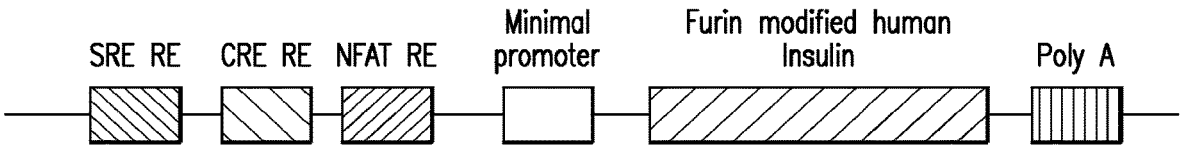


FIG. 19A

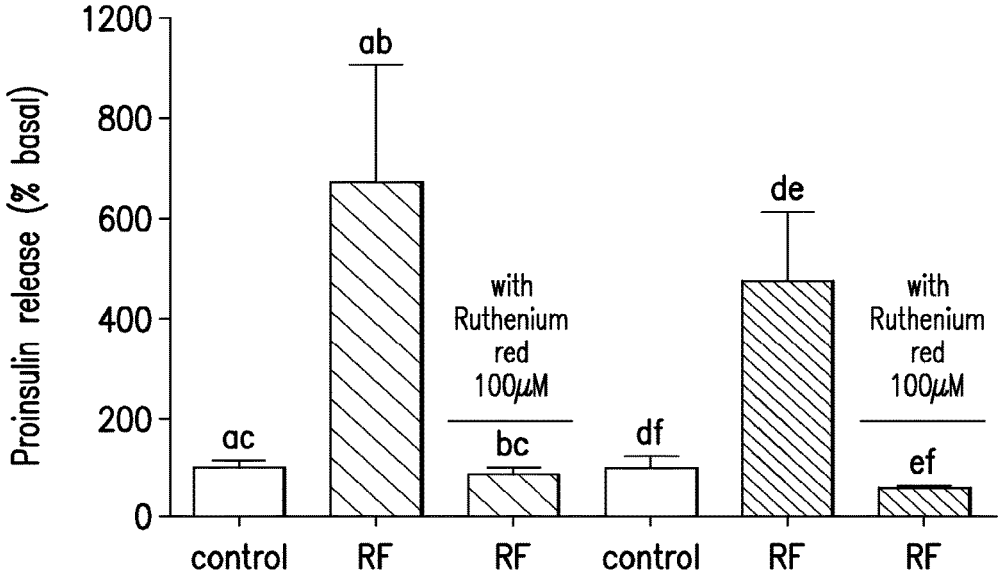


FIG. 19B

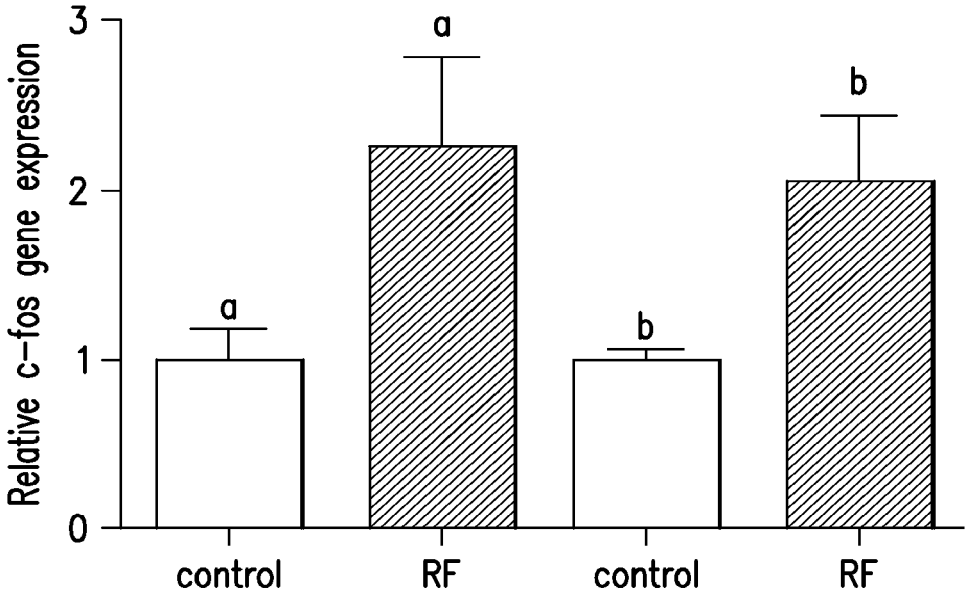


FIG. 19C

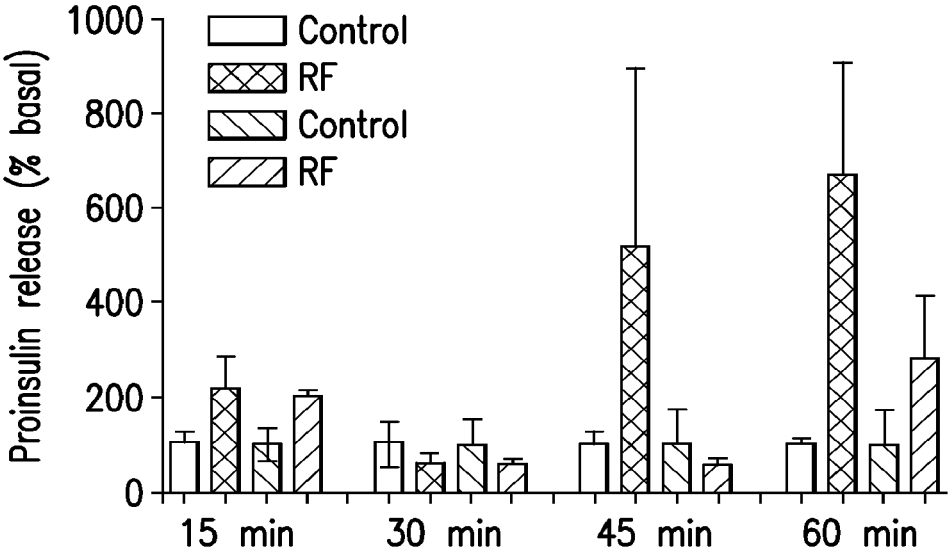


FIG. 19D

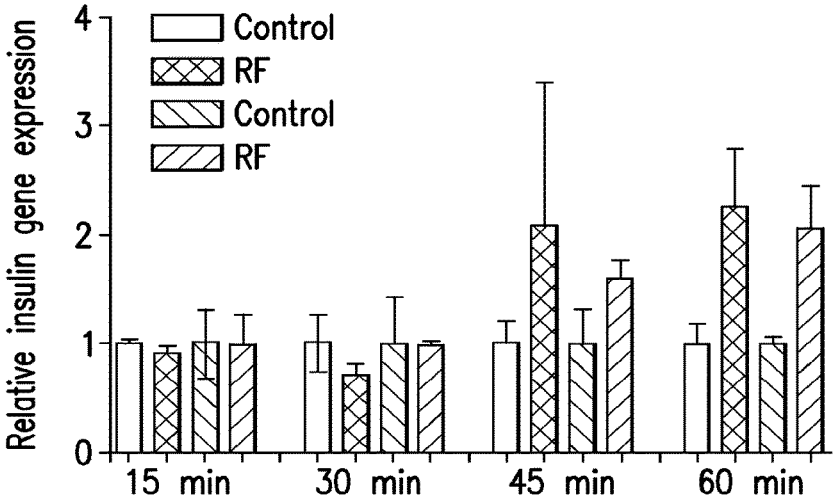


FIG. 19E

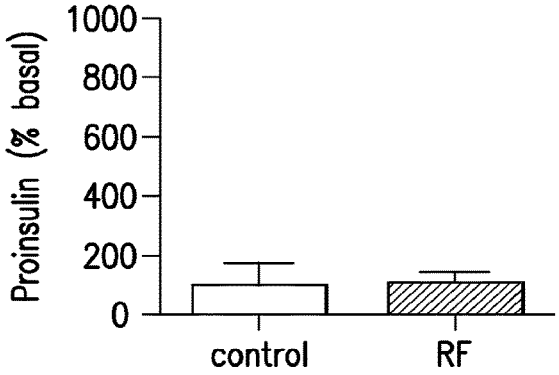


FIG. 19F

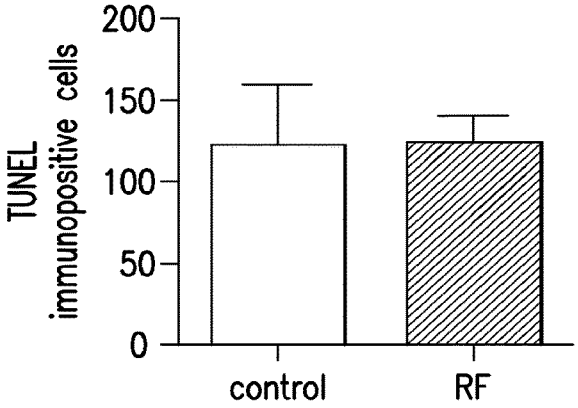


FIG. 19G

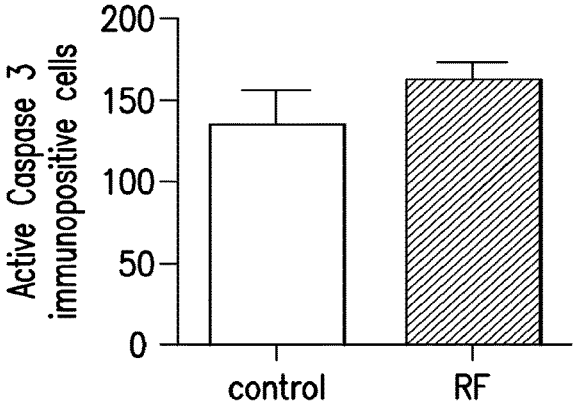


FIG. 19H

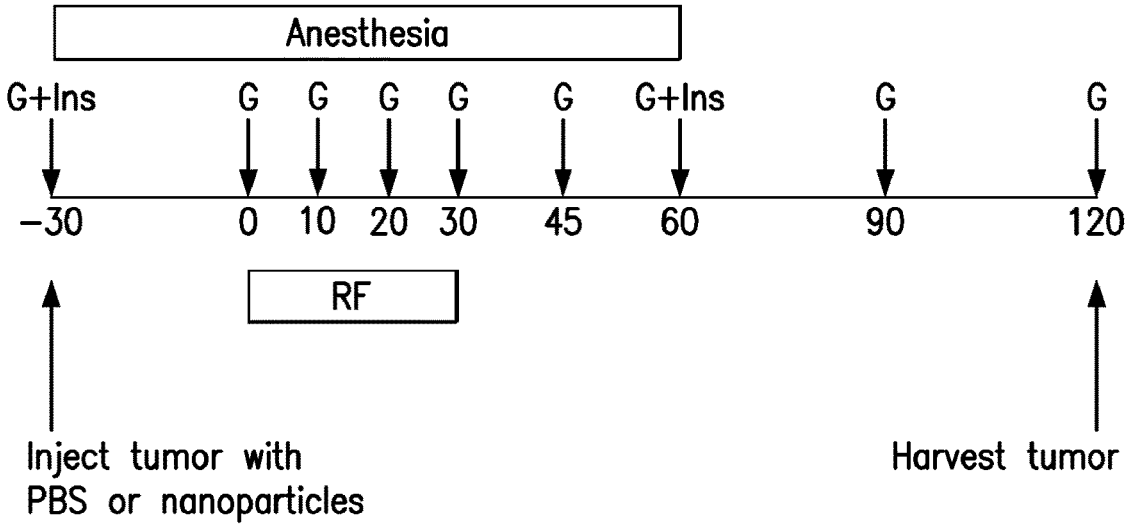


FIG. 20A

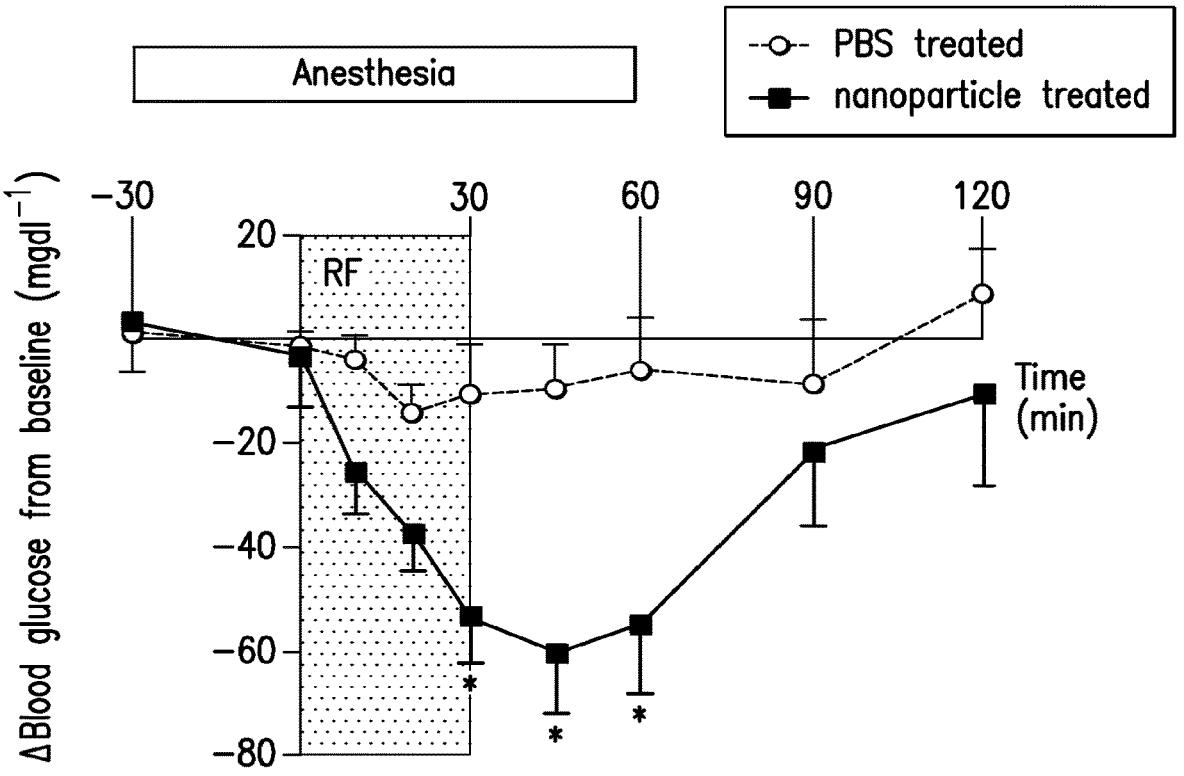


FIG. 20B

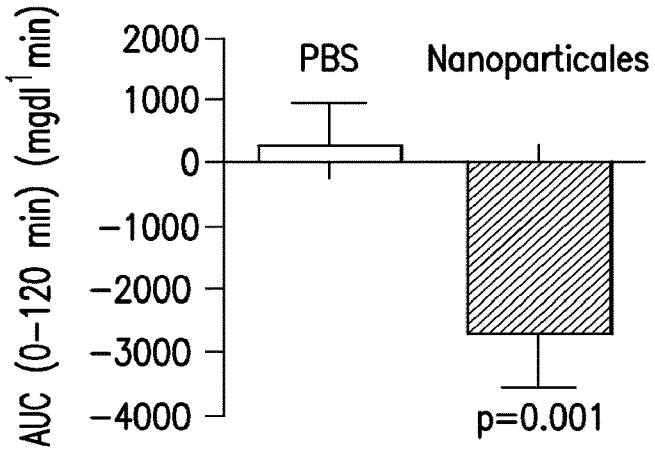


FIG. 20C

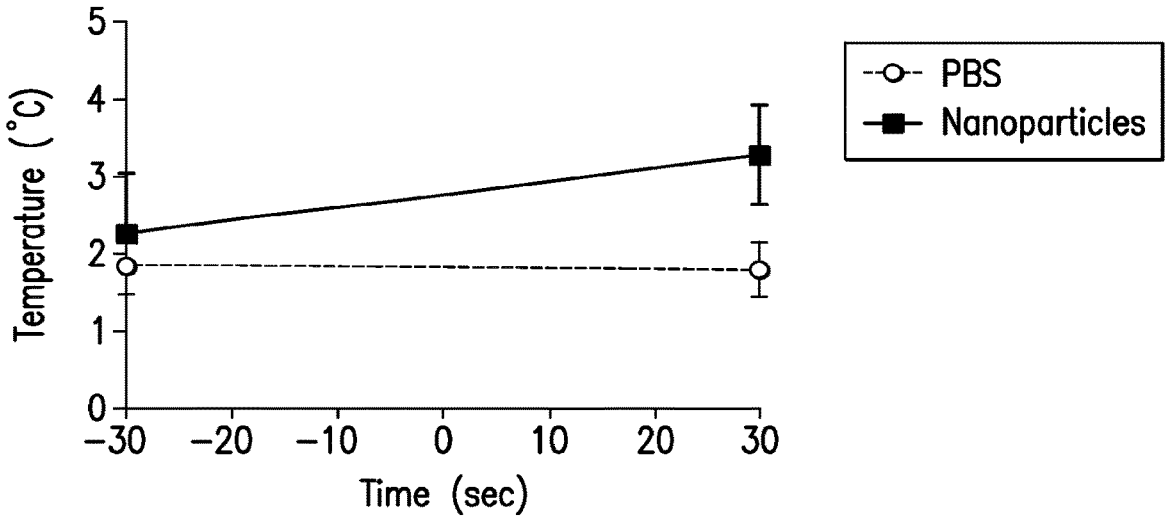


FIG. 20D

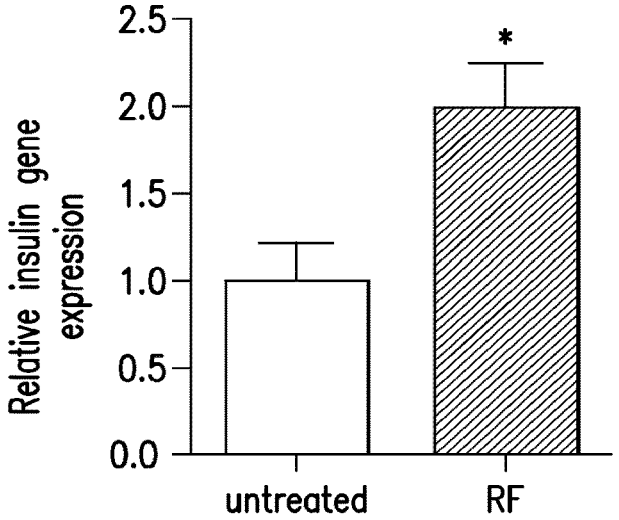


FIG. 20E

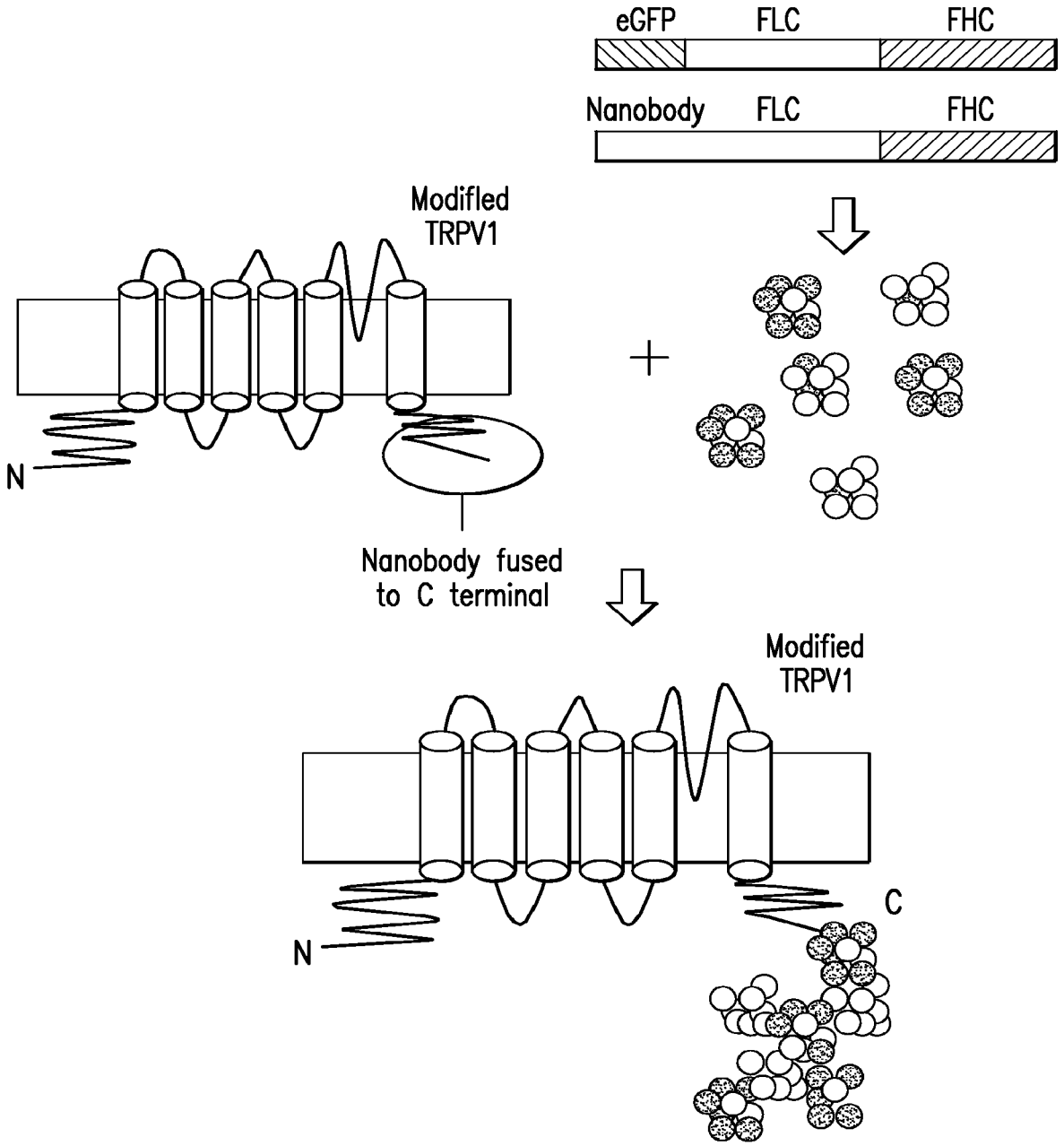

eGFP
FLC
FHC
Nanobody
FLC
FHC
Modifled
TRPV1
N
Nanobody fused
to C terminal
Modified
TRPV1
N
C

FIG. 21A

FIG. 21B

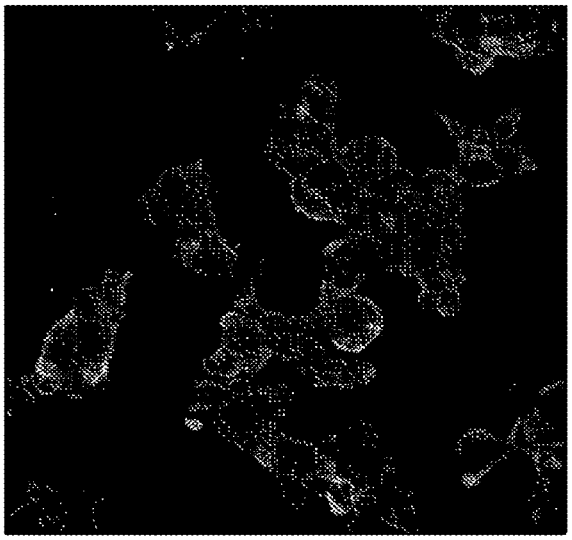


FIG. 21C

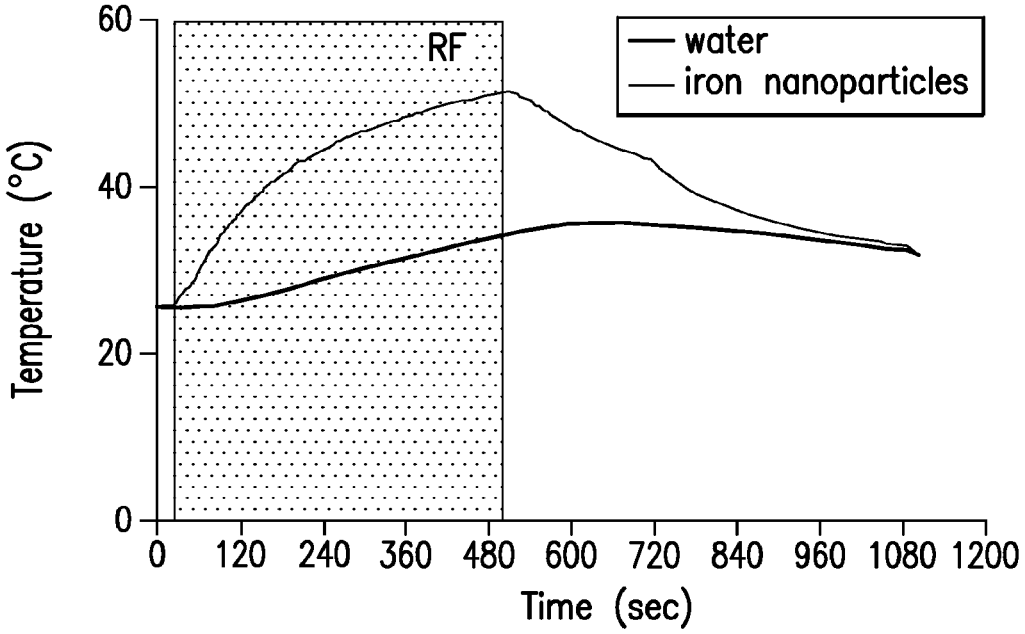


FIG. 22A

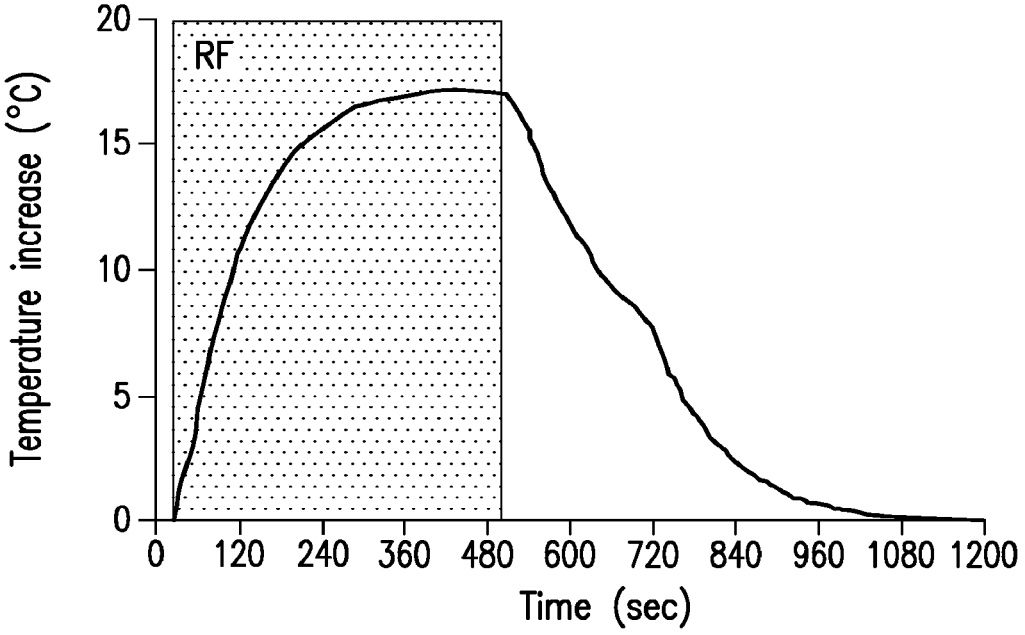


FIG. 22B

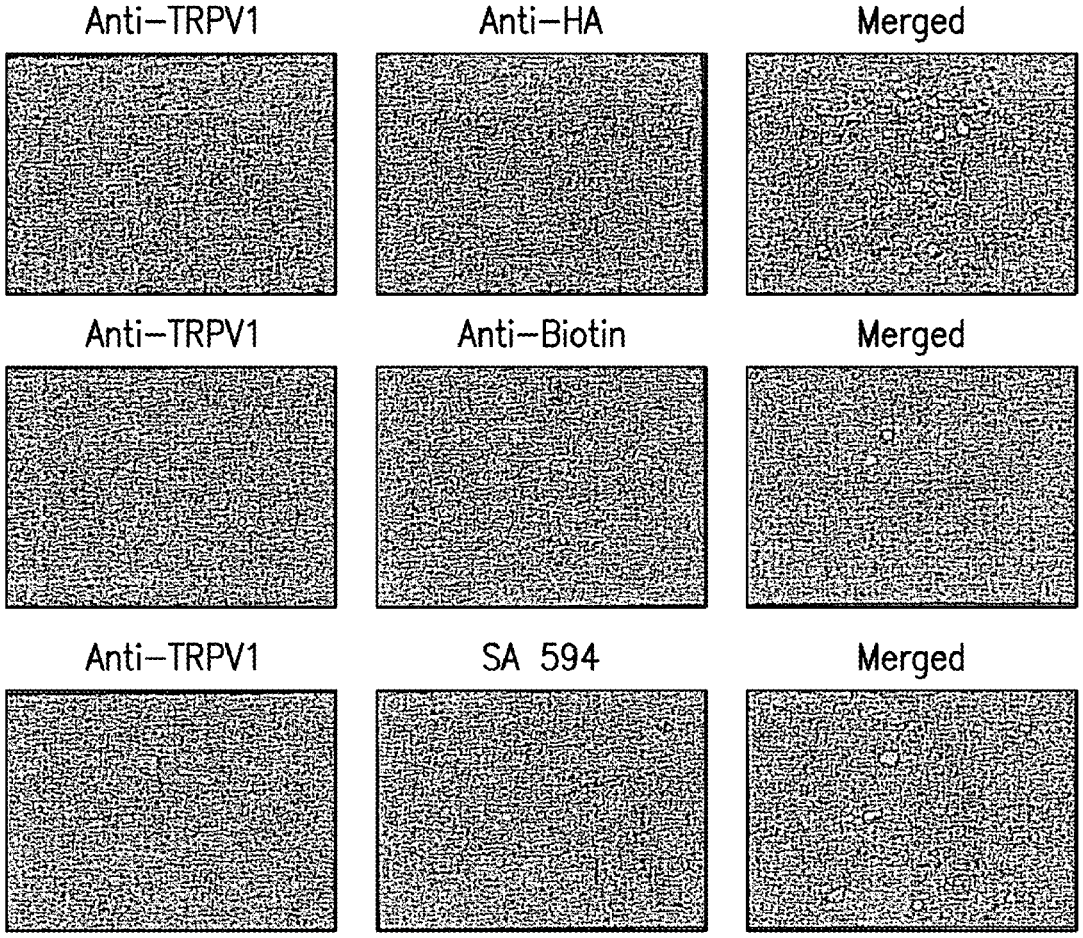


FIG. 23A

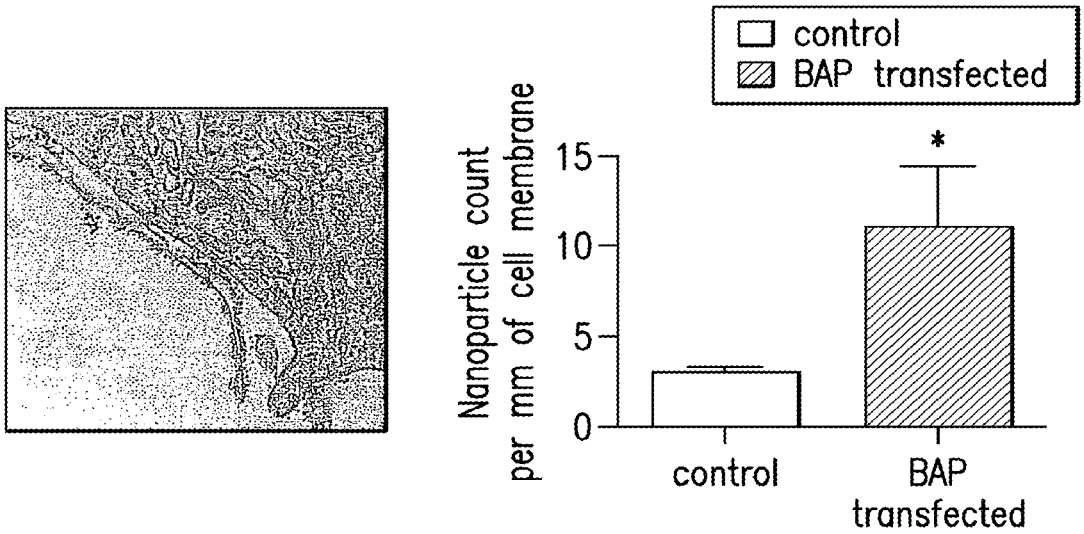


FIG. 23B

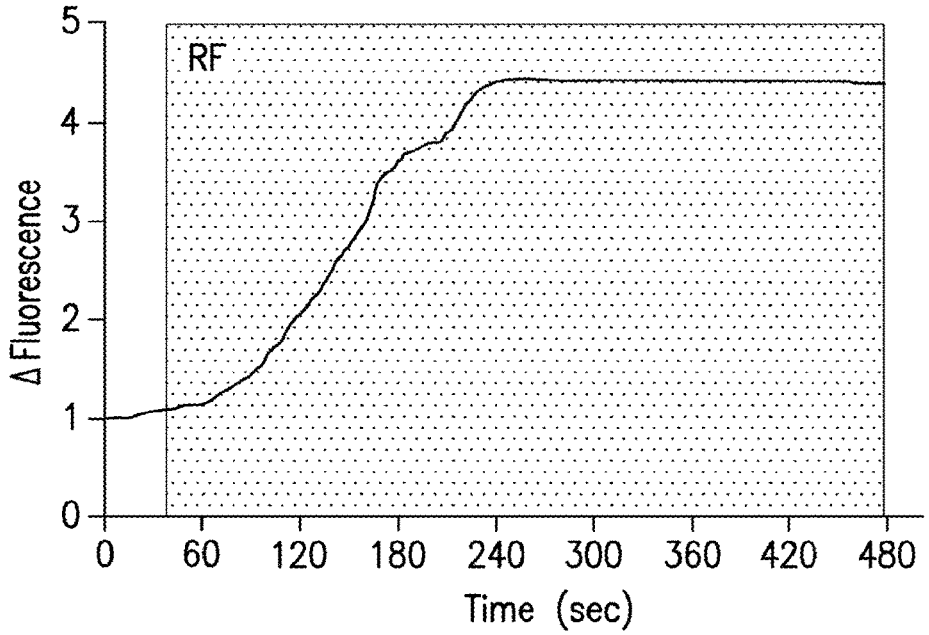


FIG. 24A

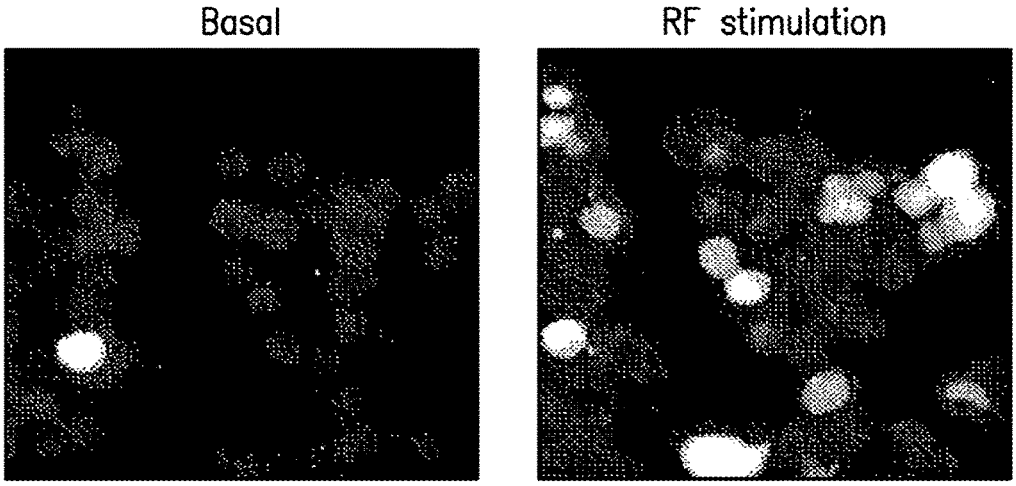


FIG. 24B

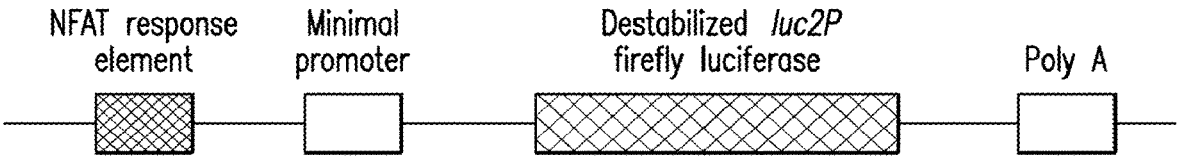


FIG. 24C

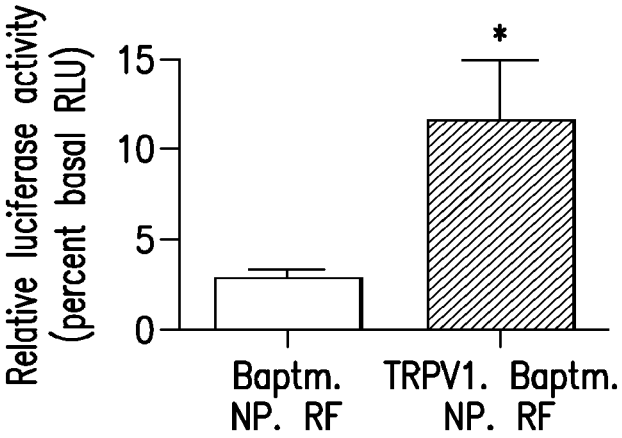


FIG. 24D

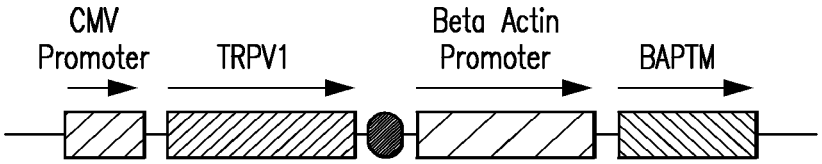


FIG. 25A

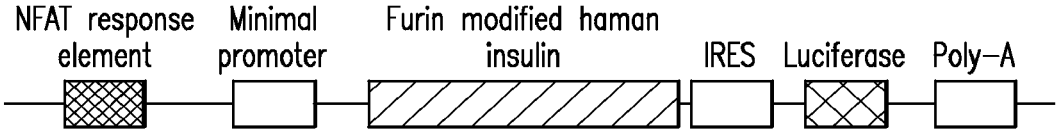


FIG. 25B

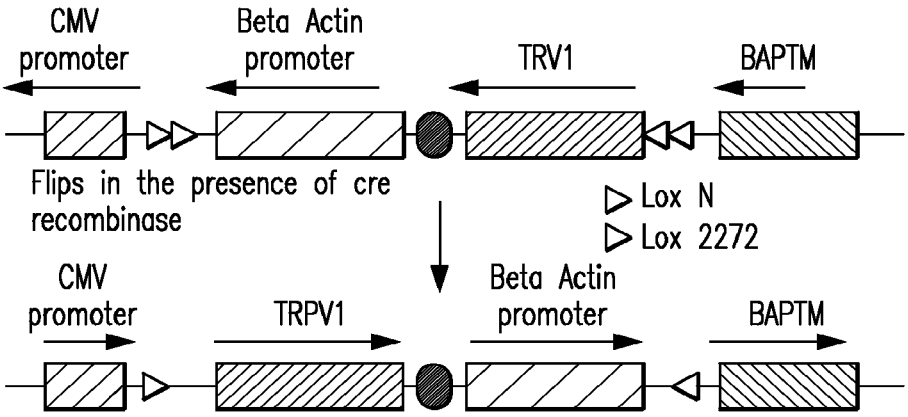


FIG. 25C

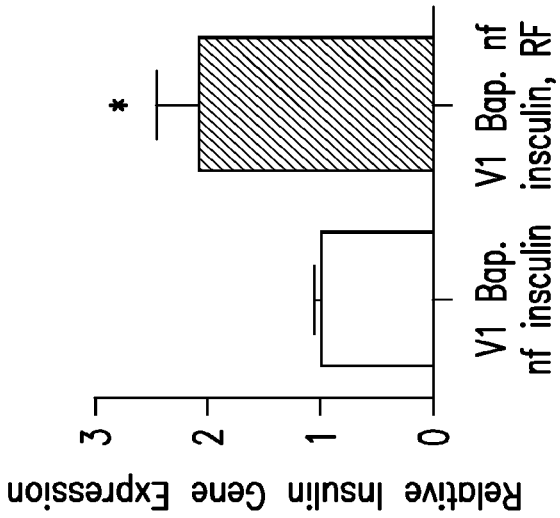


FIG. 25E

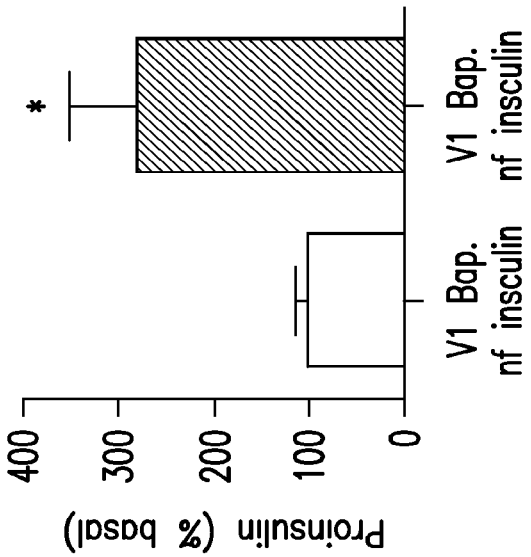
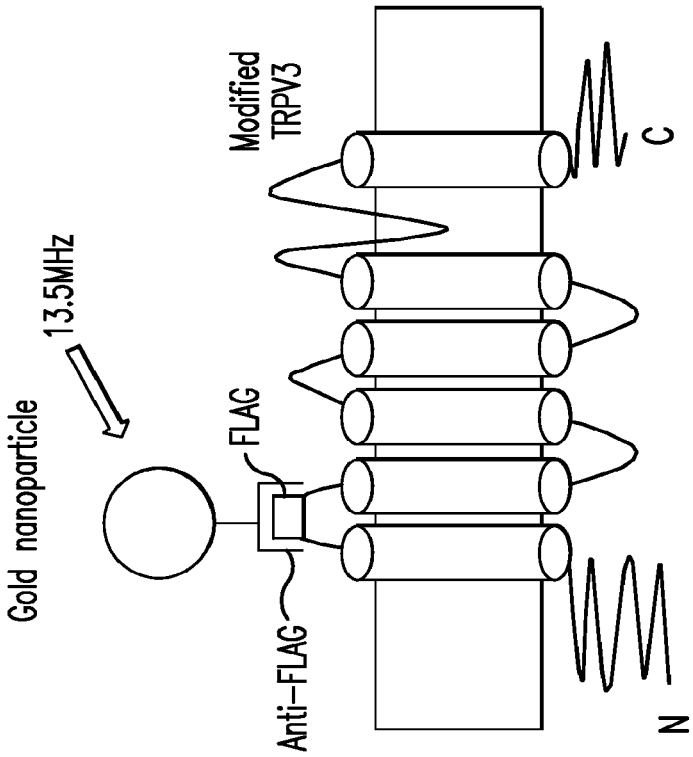


FIG. 25D



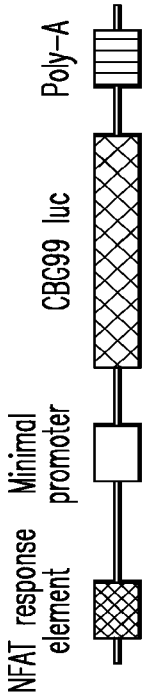
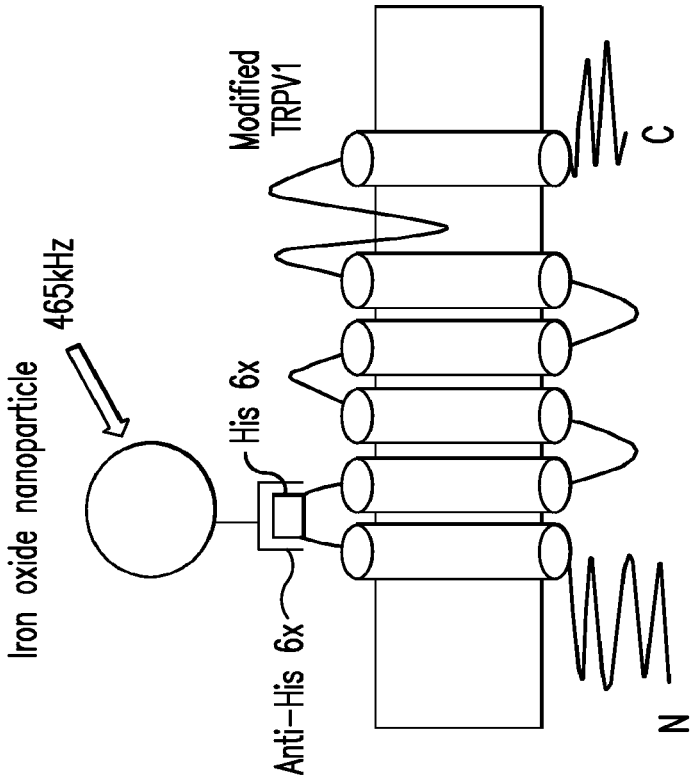


FIG. 26B



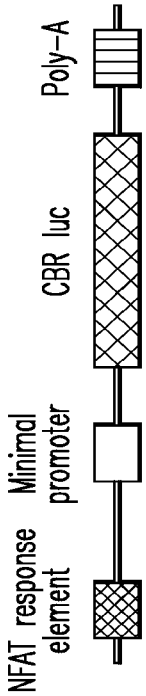


FIG. 26A

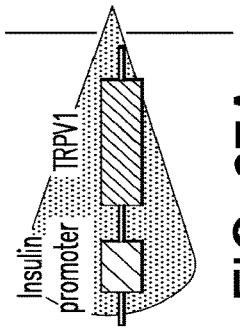


FIG. 27A

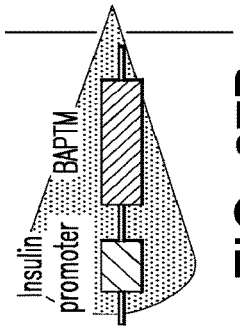


FIG. 27B

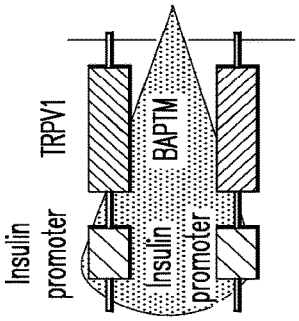


FIG. 27C

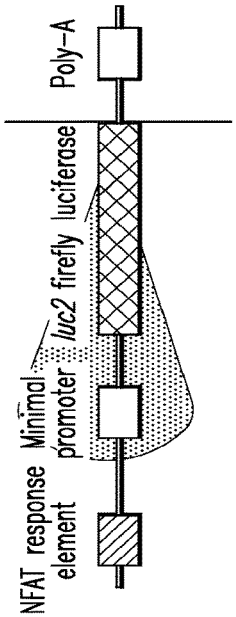
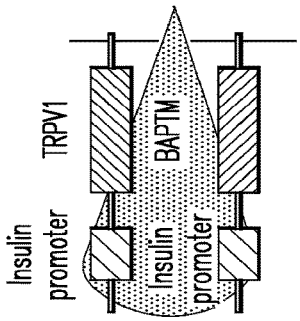


FIG. 27D



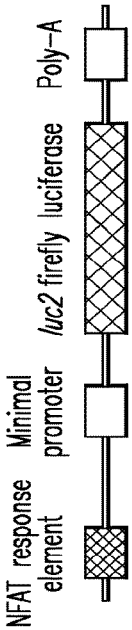


FIG. 27E

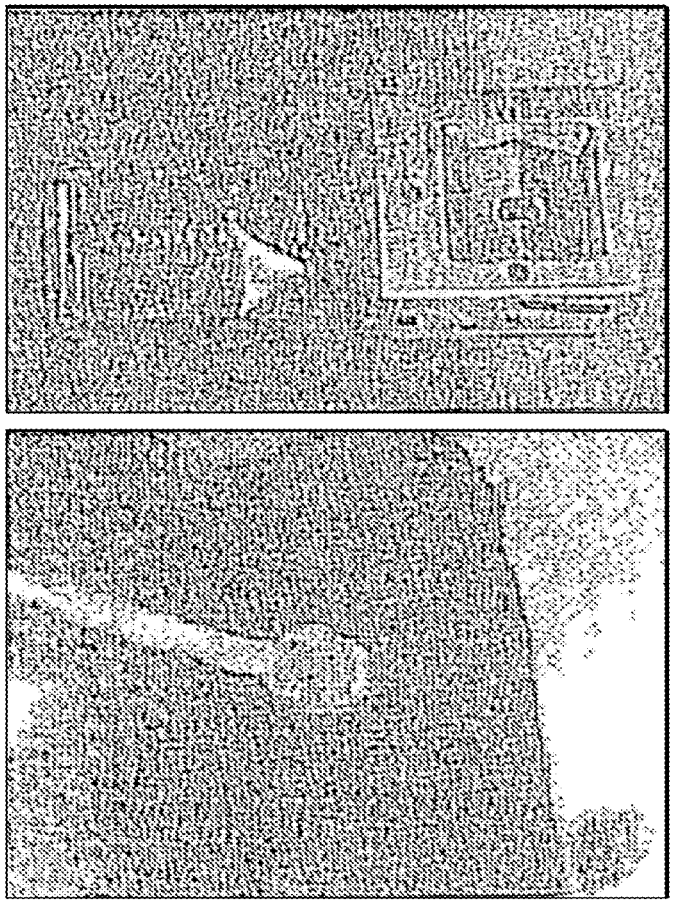


FIG. 28B

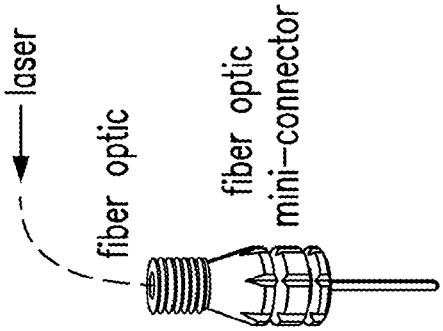


FIG. 28A

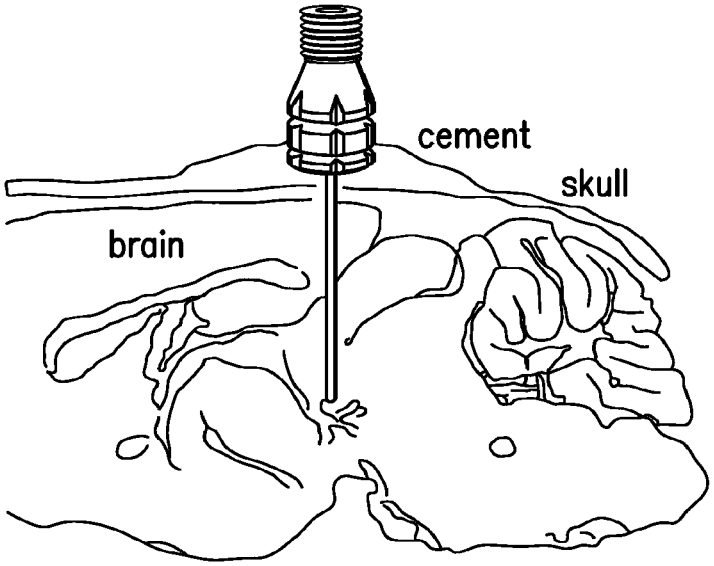


FIG. 28C

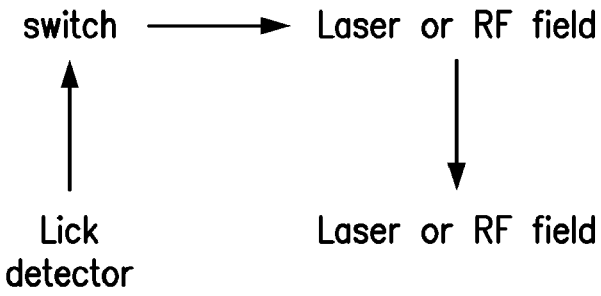


FIG. 28D

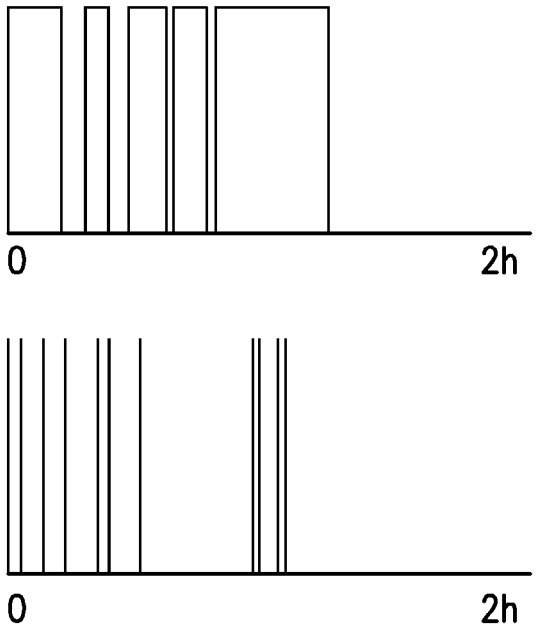


FIG. 28E

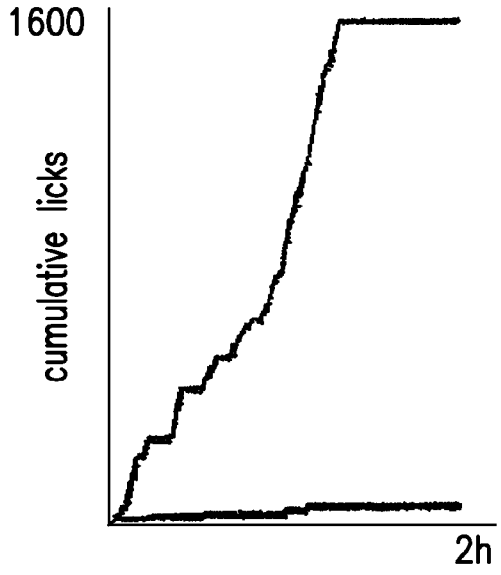


FIG. 28F

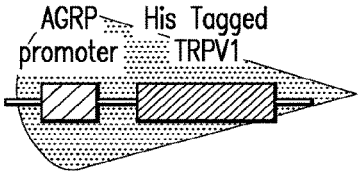


FIG. 29A

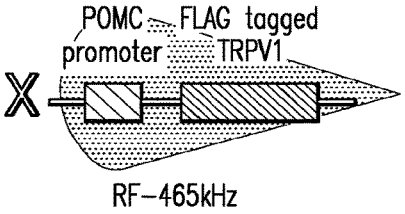


FIG. 29B

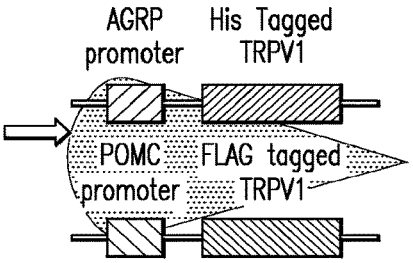


FIG. 29C

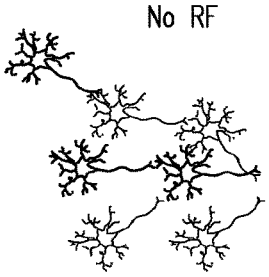


FIG. 29D

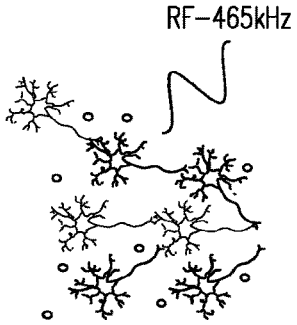


FIG. 29E

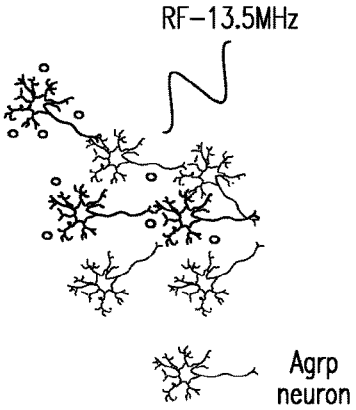


FIG. 29F

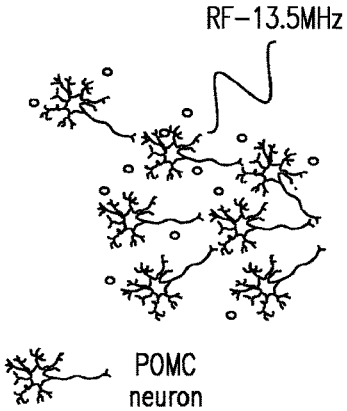


FIG. 29G

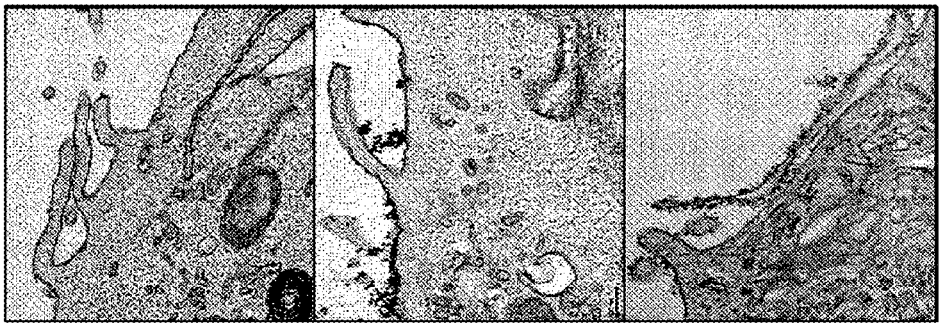


FIG. 30B

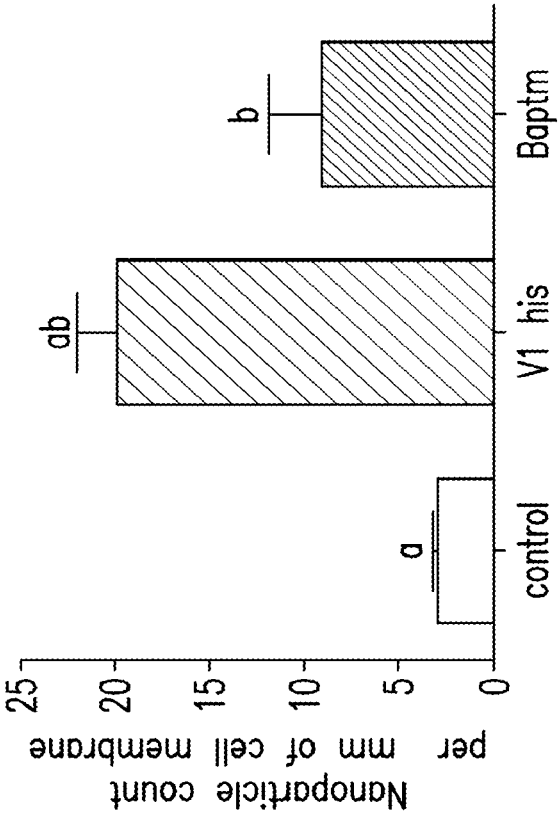


FIG. 30A

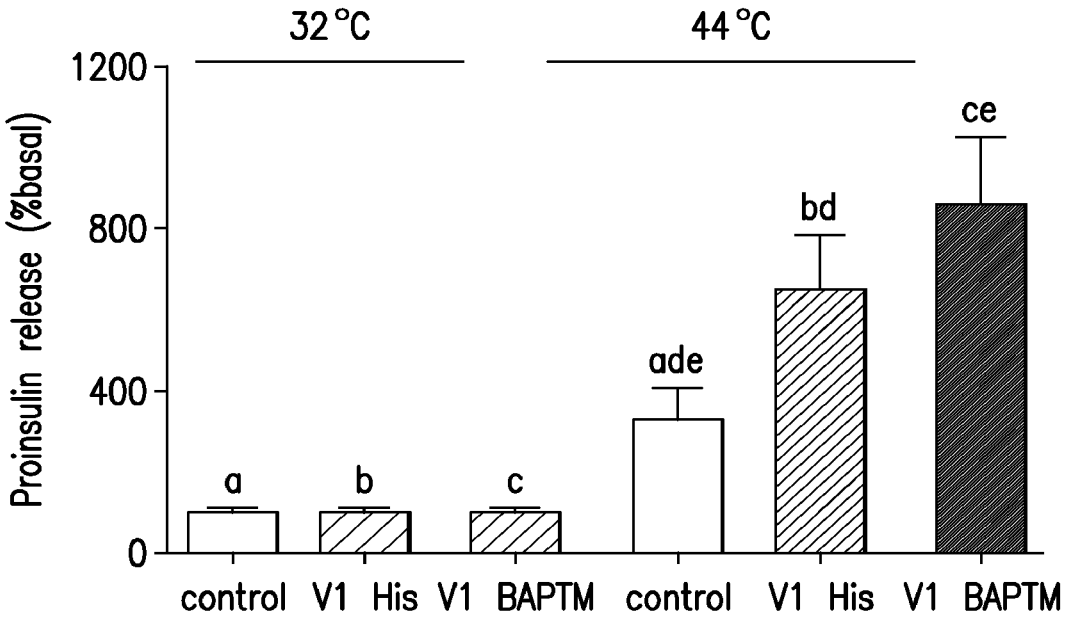

32 °C
44 °C
1200
800
400
0
Proinsulin release (%basal)
a
b
c
ade
bd
ce
control
V1
His
V1
BAPTM
control
V1
His
V1
BAPTM

FIG. 31

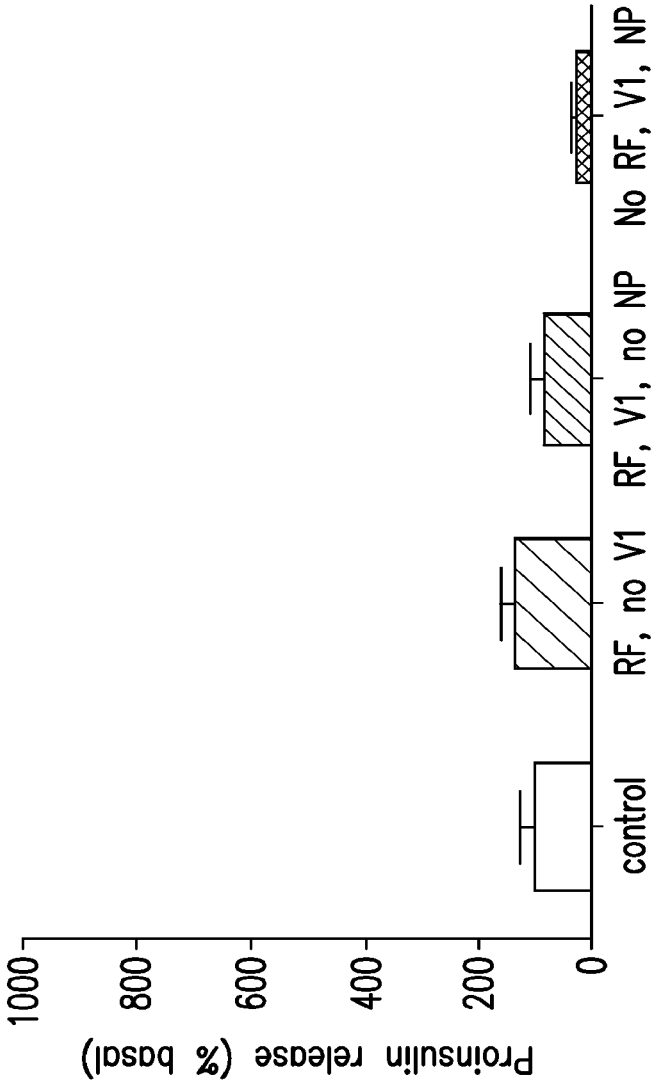

Proinsulin release (% basal)
1000
800
600
400
200
0
control
RF, no V1
RF, V1, no NP
No RF, V1, NP

FIG. 32

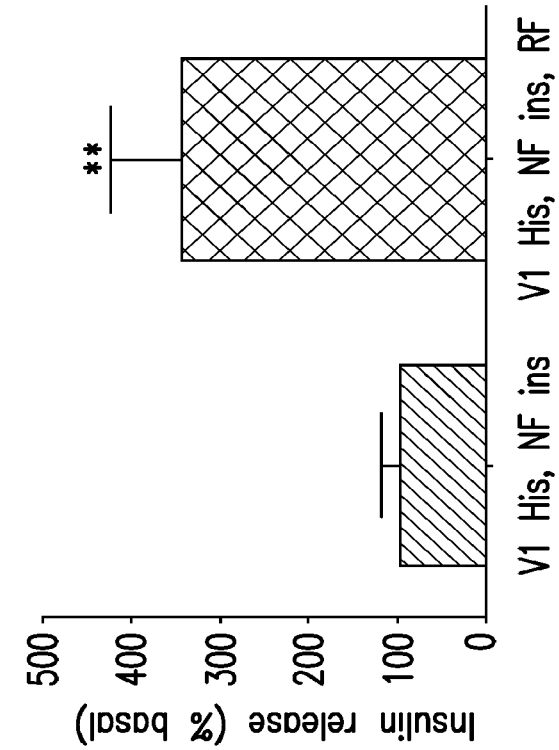


FIG. 33B

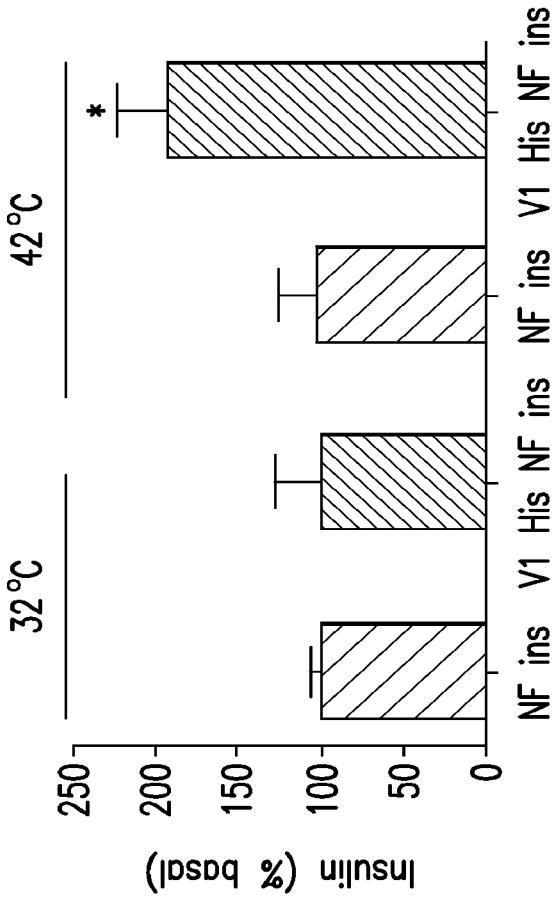


FIG. 33A

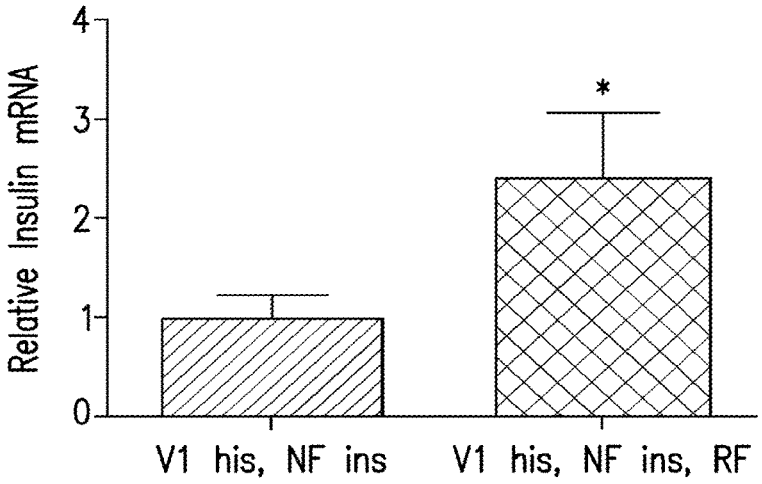


FIG. 33C

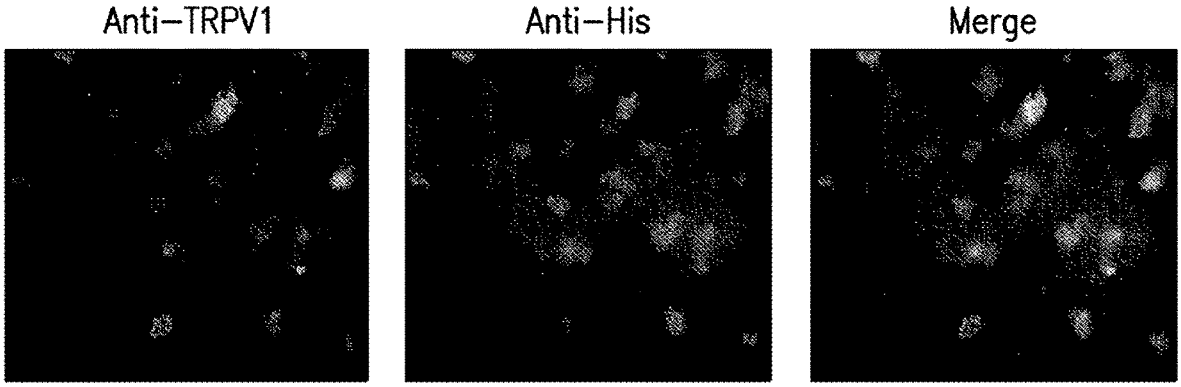


FIG. 33D

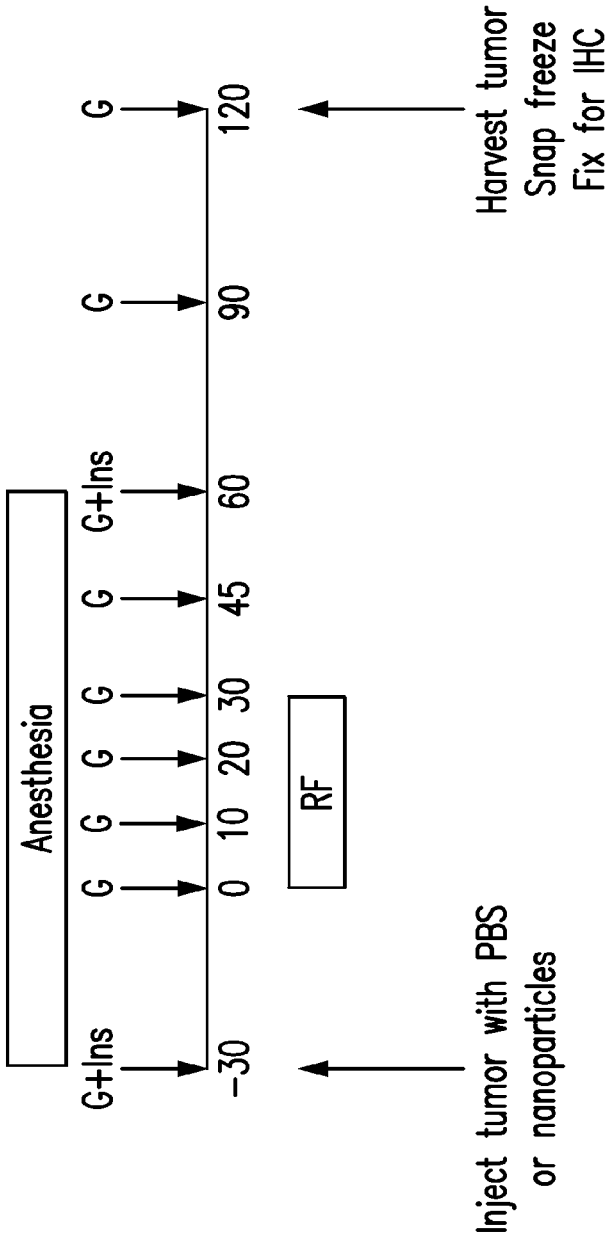

Anesthesia
G+Ins
G
G
G
G
G
G+Ins
G
G
G
−30
0
10
20
30
45
60
90
120
RF
Inject tumor with PBS
or nanoparticles
Harvest tumor
Snap freeze
Fix for IHC

FIG. 33E

FERRITIN NANOPARTICLE COMPOSITIONS AND METHODS TO MODULATE CELL ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional of U.S. application Ser. No. 15/168,950, filed on May 31, 2016, which is a continuation of U.S. application Ser. No. 14/239,427, filed on Feb. 18, 2014, which is a U.S. National Phase application of International Application No. PCT/US2012/052391, filed Aug. 24, 2012, which claims priority based on U.S. Provisional Application No. 61/526,985, filed Aug. 24, 2011, all of which are incorporated herein by reference.

The invention disclosed herein was made with United States Government support under NIH Grant No. RO1 GM095654 from the National Institutes of Health. Accordingly, the United States Government has certain rights in this invention.

FIELD OF THE INVENTION

The present invention provides methods and compositions for the remote control of cell function based on the use of radiofrequency waves to excite nanoparticles targeted to specific cell types. The cell type of interest expresses a temperature sensitive channel wherein excitation of the nanoparticles results in a localized temperature increase that is transduced into a cellular response. Such cellular responses may include, for example, increases in gene expression resulting in production of one or more physiologically active proteins. The expression of such proteins can be used to treat a variety of different inherited or acquired diseases or disorders in a subject. Accordingly, the invention provides a generic approach for treatment of any disease associated with a protein deficiency.

BACKGROUND OF THE INVENTION

The tools for dissecting the contribution of specific cells to physiological functions and particular behavior have evolved over recent years. Initial studies used electrical and chemical lesions to ablate both neurons and fibers in defined regions. Later investigations made use of direct stimulation through implanted electrodes, however, these studies were hampered by variable activation, the need for permanent implants, and tissue damage. As an alternative to these approaches, recent techniques make use of drug inducible systems to alter gene expression or ion channels to modulate cell activity (Lerchner et al., Neuron 54:35-49). By allowing the selective passage of cations or anions, families of ion channels regulate intracellular ion concentrations, which in turn modulate intracellular functions according to the cell type. The use of ion channels has many advantages; their structure and function are relatively well described; they have a rapid time course of activation, and a broad range of channels exist in mammalian and non-mammalian cells, which may be exploited in the search for the optimum means of modifying cellular activity. This approach was first validated by transgenic expression of a drug-gated channel to modify behavior, however, the time course of effects was relatively slow (hours to days) due to irreversible effects of the ligand. Recently, the non-mammalian channelrhodopsin (ChR2) gene, a light activated cation, has been employed to rapidly activate molecularly defined neurons when exposed to blue light (Boyden E S et al. 2005 Nat Neurosci 8: 1263-1268). This system gives anatomical specificity and temporal control but also has limitations. For example, there are only two variants for activation, thereby limiting the potential for combinatorial activation, and more importantly, activation in vivo requires fiber optic light delivery via implanted devices that are invasive and can interfere with behavior.

The present invention provides methods and compositions for the remote control of cell function based on the use of radiofrequency waves to excite nanoparticles targeted to specific cell types. The invention, uses Nanoparticle Induced Circuit Excitation (NICE) to, for example, regulate ion channels as a means for stimulating the activity of specific cells remotely and non-invasively.

SUMMARY OF THE INVENTION

The invention described herein utilizes Nanoparticle Induced Circuit Excitation (NICE), which encompasses compositions and methods that have been developed for stimulating the activity of specific cells remotely and non-invasively. The present invention provides methods and compositions based on the use of radiofrequency waves to excite nanoparticles targeted to specific cell types. The cell type of interest expresses a temperature sensitive channel wherein excitation of the nanoparticles results in a localized temperature increase that is transduced into a cellular response. The excitation of the nanoparticles results in a localized temperature increase that is transduced into a cellular response such as, for example, an increase in gene expression. Such increases in gene expression may result in production of one or more physiologically active proteins. The expression of such proteins can be used to treat a variety of different inherited or acquired diseases or disorders in a subject.

According to one aspect, the described invention provides a method to remotely stimulate the activity of a cell type of interest wherein the nanoparticles are externally applied. Such a method comprises: (i) administering to a cell population nanoparticles selective for the cell type of interest; and (ii) applying a radiofrequency field to remotely activate the nanoparticles. Said activation of the nanoparticles results in stimulation of the activity of the cell type of interest.

Alternatively, cells may be engineered to synthesize nanoparticles intracellularly. For example, as described herein, the iron storage protein ferritin, which forms a naturally occurring iron nanoparticle, was modified to form a ferritin fusion protein composed of a ferritin light chain fused to ferritin heavy chain with a flexible linker region. Heating of the iron core by a RF magnetic field opens the TRPV1 channel to trigger calcium entry, increasing proinsulin gene expression and triggering insulin release in vitro. This results in decrease blood glucose in vivo.

In another embodiment of the invention as described herein, modification using intracellular nanoparticles uses a modified TRPV1 with a camelid antibody to GFP fused to the N-terminal of TRPV1 and a modified ferritin fusion protein with EGFP fused to the N-terminal of ferritin light chain-linker-ferritin heavy chain. Heating of the iron core of the ferritin attached to the TRPV1 triggers calcium entry and increases proinsulin gene expression and proinsulin release in vitro.

In a non limiting embodiment of the invention, said nanoparticles may be paramagnetic nanoparticles.

According to another aspect of the invention, a method is provided to remotely stimulate the activity of a cell type of interest in a subject, the method comprising: (i) administer-

ing to the subject nanoparticles selective for the cell type of interest; and (ii) applying a radiofrequency field to remotely activate the nanoparticles. Said activation of the nanoparticles results in stimulation of the activity of the cell type of interest in a subject.

Activities of the cell that may be stimulated include, for example, cellular responses such as cell proliferation and/or differentiation, apoptosis, activation of signal transduction pathways, neuronal activation, development of long term potentiation and/or regulation of gene expression.

Further, the invention provides a method to stimulate the activity of a cell type of interest in a subject, the method comprising steps: (a) administering to the subject modified cells of interest that comprise nanoparticles that are selective for the cell type of interest; and (b) applying a radiofrequency field to remotely activate the nanoparticles. Said activation of the nanoparticles results in stimulation of the activity of the cell type of interest in a subject.

The present invention can be used in a variety of different clinical settings. For example, the technology can be used to control the expression of physiologically active proteins for used in treatment of various inherited or acquired disorders or diseases. For example, stem cells, such as induced pluripotent stem cells (iPSC) or autologous mesenchymal stem cells engineered to express NICE constructs could act as autografts enabling external control of cell function. NICE dependent calcium entry can then be used to regulate functions including hormone release, muscle contraction, or neural activity. Regulated hormone expression and release can facilitate the treatment of several endocrine conditions such as diabetes. Neuronal stimulation can be used therapeutically in several debilitating conditions such as Parkinson's disease (subthalamic stimulation) and stroke (transcranial direct current stimulation), as well as for pain relief and gastroparesis (Benabid A L. et al, 2009 Lancet Neurol 8:67-81; Schlaug G. et al. 2008 Arch Neurol 65: 1571-1576; Nnoaham K E, Kumbang J 2008 Cochrane Database Syst RevCD003222; Maranki J, Parkman H P 2007 Curr Gastroenterol Rep 9:286-294).

Functional nanoparticles, prepared using methods known to those skilled in the art, can be targeted by coating with recombinant antibodies directed to endogenous cell specific surface proteins. These applications and the approaches can be applied in animals using the NICE techniques.

Further, the methods and compositions of the invention provide a means for dissecting the contributions of defined cell populations to physiology. The present invention makes it possible to decorate different cell types with nanoparticles tuned to different frequencies, thus allowing one to simultaneously activate ensembles of defined cells even if they are in proximity. The described invention provides for selective modification of cellular function non-invasively both in vitro and in vivo. At present, there are no methods for anatomically discrete, temporally controlled, non-invasive cell activation. Such a technique allows one to study the roles of cell populations in physiological processes, in particular those functions that are, or would be, perturbed by invasive methods.

Further, the invention proves non-human transgenic animals containing different cell types that can be activated remotely through the targeting of nanoparticles to the surface of said cells. The transgenic animals provide an in vivo means for studying the contributions of defined populations of cells to physiology. Further, the transgenic animals of the invention may be used as animal model systems for the screening, identification and testing of useful therapeutic compounds.

Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Pat. Nos. 4,736,866 and 4,870,009, both by Leder et al, U.S. Pat. No. 4,873,191 by Wagner et al. and in Hogan, B., Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals.

The described invention provides, for example, methods to remotely modulate cell function in vertebrates and apply NICE to (i) modify glucose metabolism (ii) activate dopaminergic neurons in the midbrain that control reward and (iii) use a combinatorial activation scheme to regulate feeding behavior.

As described in detail below, a specific embodiment of the invention makes use of a unique combination of four components: (i) a radio frequency electromagnetic field; (ii) cell-specific expression of a nanoparticle tether; (iii) metallic/metal oxide nanoparticles; and (iv) a temperature sensitive TRPV cation channel to induce a tunable increase in intracellular calcium.

The present invention also provides pharmaceutical compositions comprising nanoparticles that are selective for a cell type expressing a temperature sensitive channel. Alternatively, pharmaceutical compositions of the invention may comprise modified cells expressing a temperature sensitive channel of interest and decorated with nanoparticles selective for said cells.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**. Nanoparticles induced cell excitation to increase insulin expression and release in vitro. Schema of nanoparticle-induced cell activation and gene expression. Antibody-coated ferrous oxide nanoparticles bind to a unique epitope, His×6, in the first extracellular loop of the temperature-sensitive TRPV1 channel. Exposure to a RF field induces local nanoparticle heating, which opens temperature-sensitive TRPV1 channels. Calcium entry triggers downstream pathways, such as activation of calcineurin, leading to dephosphorylation of NFAT and translocation to the nucleus. Here, NFAT binds to upstream response elements to initiate gene expression of a bioengineered human insulin gene. Additional calcium-dependent signal transduction pathways also stimulate gene expression via binding to SRE and CRE. P indicates a phosphate group.

FIGS. **2**A-**2**E. Heating of iron oxide nanoparticles in RF magnetic field. (**2**A) Bulk heating effects of treating iron oxide nanoparticle suspensions (1 mg/ml, 10-50 nm) in water with 465 kHz RF magnetic field. (**2**B) TEM of Ocean Nanotech (SHP-20-50) iron oxide nanoparticles and their size distribution, calculated to be 19.83±2.7 from 450 particles. (**2**C) X-ray photoelectron spectroscopy of iron oxide nanoparticle samples. Survey indicated the presence of iron, carbon, and oxygen with iron content investigated in upper inset and the presence of carboxyl groups confirmed in the lower inset. (**2**D) XRD pattern of iron oxide nanoparticles compared with JCPDS patterns #39-1346 (γ-Fe_2O_3) and #75-0033 (Fe_3O_4). (**2**E) Bulk heating effects of treating iron oxide nanoparticle suspensions (1 mg/ml, 10-30 nm) in water with 13.56 Mhz, 200 W, RF magnetic field.

FIGS. **3**A-**3**D. Nanoparticle decoration of cells in vitro. (**3**A) Nanoparticle decorationof cells in vitro. Significant nanoparticle binding to the surface of HEK293T cells expressing His tagged TRPV1 compared to untransfected cells. (**3**B) Electron micrograph of anti-His antibody coated

iron oxide nanoparticles (20 nm) binding to untransfected HEK293T cells (left panel) and HEK293 cells transfected with $TRPV1^{His}$ (right panel). Scale bar 200 nm. (**3**C) Immunoelectron micrography of anti-His antibody coated iron oxided nanoparticles (20 nm) co-localized with silver enhanced gold immunostaining for TRPV1 (10 nm particles) in transfected HEK 293T cells (left panel). There is no TRPV1 immunostaining in the absence of the primary antibody (right panel). Scale bar as indicated. (**3**D) Representative changes in Fluo-4 fluorescence after application of TRP agonist 2APB or RF treatment in HEK 293T cells transfected with $TRPV1^{His}$ and decorated with nanoparticles.

FIG. **4**. Temperature dependent release of proinsulin. Proinsulin release from HEK 293T cells transfected with calcium dependent insulin alone, $TRPV1^{His}$ and calcium dependent insulin or TRPV1 and calcium dependent insulin was examined at 32° C., below the threshold for TRPV1 activation and at 44° C., above the threshold for TRPV1 activation. Expression of $TRPV1^{His}$ and TRPV1 significantly increased proinsulin release at 44° C. compared to that from cells without TRPV1. There is no significant difference in the proinsulin release seen with TRPV His compared to unmodified TRPV1. (Same letter indicates $p<0.05$).

FIGS. **5**A-**5**G. (**5**A) Bioengineered human insulin construct. Calcium dependent insulin release is via three calcium response elements: serum response element (SRE), cyclic AMP response element (CRE) and nuclear factor of activated T-cell response element (NFAT RE) and a minimal promoter upstream of a furin sensitive human insulin cDNA. (**5**B) RF treatment does not change proinsulin release from cells expressing the calcium dependent insulin gene from cells with $TRPV^{His}$, calcium dependent human insulin and nanoparticles in the absence of RF treatment, from cells expressing TRPV1 and calcium dependent human insulin treated with RF but in the absence of nanoparticles, or from cells treated with RF expressing calcium dependent human insulin and binding nanoparticles via a nanoparticle tether comprised of a platelet derived growth factor receptor transmembrane domain with fused extracellular biotin acceptor [protein but in the absence of TRPV1. (**5**C) The effects of nanoparticle heating are cell specific. Cells transfected with a nanoparticle tether, BAPTM, and mixed with cells transfected with TRPV1 and calcium dependent human insulin show no increase in proinsulin release with RF treatment. (**5**D) Translocation of NFAT1 with RF treatment. HEK cells transfected with $TRPV1^{His}$/calcium dependent human insulin incubated with anti-His iron oxide nanoparticles show almost exclusively cytoplasmic NFATimmunostaining without RF treatment (control, upper panels). RF treatment results in NFAT staining in both the cytoplasm and nucleus of the cells (RF, lower panels). (**5**E) Effect of calcineurin inhibitor on RF dependent proinsulin release. Proinsulin release from RF treated HEK cells transfected with $TRPV1^{His}$/calcium dependent human insulin incubated with anti-His oxide nanoparticles was blocked by preincubation with Tacrolimus (100 nM). There is no difference apoptotic cells incubated with increasing concentrations of nanoparticles as assessed by TUNEL count (**5**F) are activated Caspase-3 count (**5**G) between untreated and RF treated cells is transfected with $TRPV1^{His}$.

FIGS. **6**A-**6**B. (**6**A) RF treatment increases proinsulin release and insulin gene expression in vitro. Nanoparticle-decorated HEK293T cells transfected with $TRPV1^{His}$ and calcium-dependent insulin show a significant increase in proinsulin release and insulin gene expression with RF treatment that is blocked by the TRP antagonist ruthenium red. (Columns marked with the same letter indicate significance, $P<0.05$. Error bars indicate SEM) (**6**B) Time sources of proinsulin release and insulin gene expression from nanoparticle-decorated HEK293T cells transfected with $TRPV1^{His}$ and calcium-dependent insulin with RF treatment.

FIGS. **7**A-**7**D. Expression of constructs and RF dependent proinsulin release from ES cells. (**7**A) Expression of insulin in ES cell clones: Quantitative PCR measured expression of human insulin in 3 ES cell clones (4, 6 and 7) electroporated with $TRPV1^{His}$ and Ca^{2+}-dependent human insulin construct along with cells stably expressing TRPV1 alone, Ca^{2+}-dependent human insulin construct alone or wild-type ES cells. (**7**B) Expression of TRPV1 in ES cell clones: Quantitative PCR measured expression of TRPV1 in 3 ES cell clones (4, 6 and 7) electroporated with $TRPV1^{His}$ and Ca^{2+}-dependent human insulin construct along with cells stably expressing TRPV1 alone, Cat^{2+}-dependent human insulin construct alone or wild-type ES cells. (**7**C) Immunohistochemistry for TRPV1 (upper panels) or His (lower panels) in wild-type cells (left panels), cells stably expressing $TRPV1^{His}$ (middle panels) or ES clone 7 (right panels). (**7**D) RF dependent pro insulin release from ES cells. ES clone 7 expressing $TRPV1^{His}$ and Cat^{2+}-dependent human insulin incubated with iron oxide nanoparticles show a significant increase in proinsulin release in response to RF treatment (same letter indicates $p<0.05$).

FIGS. **8**A-**8**G depict dual component system for cell activation. (**8**A) Schema of dual component system. Streptavidin coated iron oxide nanoparticles bind biotin on a cell surface biotin acceptor protein fused to a transmembrane domain (BAPTM). Exposure to an RF field induces local heating, which opens TRPV1 channels. Calcium entry triggers downstream processes as before. (**8**B) Nanoparticle binding to the surface of HEK 293 T cells expressing TRPV1 and BAPTM is increased compared to untransfected cells ($p=0.09$). (**8**C) Representative changes in Fluo-4 fluorescence after application of TRP agonist 2APB or RF treatment in nanoparticle decorated HEK 293 T cells transfected with dual component system. (**8**D) RF treatment increases proinsulin release in vitro from HEK 293T cells transfected with TRPV1, BAPTM and calcium dependent human insulin. This is blocked by Ruthenium red. (Same letter indicates $p<0.05$). (**8**E) RF treatment increases insulin gene expression in vitro in cells with TRPV1, BAPTM and calcium dependent human insulin and is blocked by Ruthenium red. (**8**F) Time course of proinsulin release with RF treatment from HEK293T cells transfected with TRPV1, BAPTM and calcium dependent human insulin. (**8**G) Time course of insulin gene expression with RF treatment in cells transfected with TRPV1, BAPTM and calcium dependent human insulin.

FIGS. **9**A-**9**F. In vitro and in vivo studies on PC12 $TRPV1^{His}$/insulin stable cell line. (**9**A) Proinsulin release from PC12 cells stably expressing $TRPV1^{His}$ and calcium dependent human insulin was significantly increased by a temperature above the threshold for TRPV1 activation (Same letter indicates $p<0.05$). (**9**B) RF treatment significantly increased proinsulin release from PC12 cells stably expressing $TRPV1^{His}$ and calcium dependent human insulin. (Same letter indicates $p<0.01$). (**9**C) RF treatment significantly increases insulin gene expression in PC12 cells stably expressing $TRPV1^{His}$ and calcium dependent human insulin (Same letter indicates $p<0.05$). (**9**D) Time course of proinsulin release from PC12 cells stably expressing $TRPV1^{His}$ and calcium dependent human insulin. RF treatment for 15

minutes significantly increased proinsulin release. (**9**E) Serial blood glucose measurement in nude mice injected with PC12 cells expressing TRPV1^{His} and calcium dependent human insulin to form a subcutaneous tumor. (**9**F) Immunohistochemistry for TRPV1 and His epitope tag in sections from tumors formed following subcutaneous injection of PC12 cells stably expressing TRPV1^{His} and calcium dependent human insulin.

FIGS. **10**A-**10**D. Nanoparticle regulation of blood glucose in vivo. (**10**A) Effects of RF treatment on blood glucose in PBS and nanoparticle-treated mice with tumors expressing TRPV1^{His} and calcium-dependent human insulin. RF treatment significantly reduces blood glucose in nanoparticle-treated mice compared with that of PBS-treated mice. (Asterisks indicate P<0.05. Error bars indicated SEM.) (**10**B) RF treatment of mice with tumors expressing TRPV1^{His} and calcium-dependent human insulin injected with nanoparticles significantly reduces blood glucose over the course of the study as assessed by the area under the curve. There is no effect in mice with tumors expressing calcium-dependent insulin alone without TRPV1^{His} (same letter indicates P<0.05.) (**10**C) Plasma insulin is significantly increased by RF treatment in nanoparticle-treated but not PBS-treated mice with tumors expressing TRPV1^{His}. (Same letter indicates P<0.05). (**10**D) Insulin gene expression is significantly increased in the tumors expressing TRPV1^{His} and calcium-dependent human insulin treated with nanoparticles and RF magnetic field but not in tumors expressing calcium-dependent human insulin alone without TRPV1^{His}.

FIGS. **11**A-**11**F. Nanoparticle regulation of blood glucose in vivo. (**11**A) Protocol for assessment of effects of RF treatment on blood glucose in mice bearing tumors expressing TRPV1^{His} and calcium dependent human insulin. At time −30 min, mice are anesthetized and injected with PBS or nanoparticles. RF stimulation begins at time 0 and continues for 30 mins. Mice remain anesthetized for a further 30 mins. Samples for plasma insulin are taken at −30 and +30 mins and samples for blood glucose are taken before, during and after RF stimulation. (**11**B) Expression of c-fos gene in tumors showed no difference in levels between control (untreated) and RF treated tumors. (**11**C) No increase in apoptotic cells from nanoparticle and RF treated tumors as assessed by TUNEL. (**11**D) No increase in apoptotic cells from nanoparticle and RF treated tumors as assessed by immunohistochemistry (IHC) for activated Caspase-3. (**11**E) Effects of RF treatment on blood glucose in PBS and nanoparticle treated mice with tumors expressing TRPV1^{His} and calcium dependent human insulin. RF treatment significant reduces blood glucose in nanoparticle treated mice compared to PBS treated mice in both the first and second study separated by a week. (Asterisk indicates p<0.05.) (**11**F) Cumulative blood glucose change, measured by area under the curve, shows a significant decrease in nanoparticle treated mice compared to PBS treated mice in both the first and second study. There is no significant difference between the AUC for the nanoparticle studies.

FIGS. **12**A-**12**D. Effect of NICE in the absence of TRPV1, absence of anti-His antibodies and temperature studies in vivo. (**12**A) Effect of RF stimulation on blood glucose in PBS and nanoparticle treated mice bearing tumors expressing calcium dependent insulin gene without TRPV1. (**12**B) Effect of RF stimulation on blood glucose in mice treated with PBS or nanoparticles which have not been conjugated to anti-His antibody. (**12**C) Thermal imaging using an infrared camera on mouse with tumor expressing TRPV1^{His} and calcium dependent human insulin injected with iron oxide nanoparticles before (left panel) and after (right panel) RF magnetic field treatment. (**12**D) Core body temperature and intra-tumor temperature recordings from mice with TRPV1^{His} expressing tumors following nanoparticle injection and RF treatment. There is no difference in the intratumoral temperature achieved with RF treatment in the tumors of mice with TRPV1^{His} and insulin expression compared to the tumors of mice with insulin expression but without TRPV1^{His} expression.

FIGS. **13**A-**13**C. Intracellular nanoparticle synthesis and cell activation. (**13**A) Schema of intracellular nanoparticle synthesis and cell activation. A ferritin fusion protein is composed of a ferritin light chain fused to ferritin heavy chain with a flexible linker region. Heating of the iron core by a RF magnetic field opens the TRPV1 channel to trigger calcium entry, as previously described. (**13**B) RF treatment increases proinsulin release in vitro. HEK293 T cells transiently transfected with TRPV1, ferritin fusion protein, and calcium-dependent human insulin show a significant increase in proinsulin release in response to RF treatment. (Same letter indicates significance, P<0.05.) RF treatment does not increase proinsulin release from cells expressing ferritin in the absence of TRPV1. (**13**C) RF treatment increases insulin gene expression in vitro. Insulin gene expression is significantly increased by RF treatment in cells transfected with TRPV1, ferritin fusion protein, and calcium-dependent human insulin. (Same letter indicates significance, P<0.05). RF treatment does not increase insulin gene expression in cells expressing ferritin fusion protein in the absence of TRPV1.

FIGS. **14**A-**14**B. Expression of Ferritin fusion protein in vitro. (**14**A) Ferritin expression as shown by IHC for ferritin light chain. (**14**B) Electron micrograph of iron loaded ferritin in transfected cells. Scale bar 200 nm.

FIG. **15**. Release of proinsulin with RF (465 kHz) from 293 cells transfected with TRPV1 and myristoylated ferritin fusion protein (mFerritin), transfected with TRPV1 with n-terminal fusion of camelid antibody to EGFP (vhh-TRPV1) and EGFP fused to ferritin fusion protein and transfected with TRPV1 with n-terminal fusion of camelid antibody to EGFP (vhh-TRPV1), EGFP fused to ferritin fusion protein and camelid antibody fused to ferritin fusion protein along with calcium dependent insulin gene.

FIGS. **16**A-**16**B. Release of proinsulin from (**16**A) embryonic stem cells from C57BL6 mice expressing TRPV1, myristoylated ferritin fusion protein and calcium dependent insulin, decorated with nanoparticles and treated with RF and (**16**B) mesenchymal stem cells from C5BL6 mice expressing TRPV1, myristoylated ferritin fusion protein and calcium dependent insulin and treated with RF.

FIG. **17**. Regulation of blood glucose in wild-type mice. C57BL6 mice received in injection of replication deficient adenovirus expressing TRPV1, myristoylated ferritin fusion protein (mferritin) and calcium dependent insulin or adenovirus expressing LacZ. Two weeks after injection, mice were fasted overnight and anesthetized then treated with RF for 1 hour and blood glucose monitored. RF treatment of TRPV1/mferritinicalcium dependent insulin significantly reduced blood glucose compared to baseline and compared to either RF treated LacZ expressing mice or mice expressing TRPV1/mferritin/calcium dependent insulin without RF treatment.

FIGS. **18**A-**18**B. (**18**A) Change in blood glucose and (**18**B) change in blood glucose expressed as area under curve in nude mice injected with mesenchymal stem cells

alone (control) and treated with RF or mesenchymal stem cells expressing TRPV1, mferritin and calcium dependent insulin and treated with RF.

FIGS. **19**A-**19**H. (**19**A) A synthetic promoter comprised of three calcium response elements: serum response element (SRE), cyclic AMP response element (CRE) and nuclear factor of activated T-cell response element (NFAT RE) and a minimal promoter were cloned upstream of a modified, furin sensitive insulin cDNA. HEK 293t cells expressing calcium dependent human insulin and either TRPV1His or TRPV1 BAP were decorated with functionalized IO nanoparticles. Applying a RF magnetic field to nanoparticle-decorated cells expressing TRPV1His or TRPV1 BAP and calcium regulated furin sensitive insulin significantly increased proinsulin release (**19**B) and insulin gene expression (**19**C). The increases in proinsulin release are blocked by the non-specific TRP channel inhibitor, ruthenium red. There was a trend towards an increase in proinsulin release after 15 mins of RF treatment, presumably initially through the release of preformed insulin containing vesicles and with a significant increase in release at 1 hour (**19**D), whilst insulin gene expression begins to increase after 45 minutes and also becomes significant at 1 hour (**19**E). The effects of RF dependent heating of IO nanoparticles were confined to decorated cells since there was no release of proinsulin when cells expressing BAPTM as a nanoparticle tether are mixed with, and therefore adjacent to, cells expressing TRPV1 and calcium regulated furin sensitive insulin (**19**F). This time course is similar to the expression of c-fos, a gene whose expression is also calcium dependent. To assess cell viability, immunohistochemistry was used to quantify two markers of apoptosis—active caspase 3 and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL). No differences in immunopositive cell counts were observed between TRPV1His transfected 239t cells treated with nanoparticles alone and those treated with nanoparticles and RF magnetic field application (**19**G and **19**H).

FIGS. **20**A-**20**E show the effect of NICE in vivo. (**20**A) Protocol to examine the effect of RF on blood glucose and insulin in vehicle or nanoparticle injected TRPV1/NFAT-insulin tumors in nude mice. (**20**B) Effect of RF on blood glucose in vehicle (PBS) or nanoparticle injected mice. A significant difference in blood glucose is seen at 30, 45 and 60 minutes. (**20**C) Assessment of area under the curve for circulating blood glucose shows a significant difference between PBS and nanoparticle treated groups between 0 and 120 minutes. (**20**D) Circulating insulin levels increase significantly in nanoparticle treated mice. (**20**E) Insulin gene expression, as assessed by qPCR, is significantly increased in RF treated tumors.

FIGS. **21**A-**21**C show a schema of intracellular nanoparticle synthesis using ferritin chimeras. (**21**A) Iron binding chimeric ferritin peptides composed of ferritin light chain (FLC) and ferritin heavy chain (FHC) with a flexible linker sequence (pink box) are fused to either EGFP (green box) or the high affinity camelid anti-GFP antibody (yellow box). When these are expressed they form ferritin complexes with either EGFP or nanobody at the surface. The nanobody peptide is also fused to the intracellular C terminal of the temperature sensitive calcium channel, TRPV1. Expression of all three components in the cell results in an iron containing ferritin aggregate attached to the intracellular C terminal of TRPV1. (**21**B) Electron microscopy image of chimeric ferritin complexes (arrows) in 293t cells transfected with egfp-chimeric ferritin and nanobody-chimeric ferritin. (**21**C) Cell surface expression of HA-tagged nanobody fused to TRPV1 in transfected 293t cells.

FIGS. **22**A-**22**B show heating of iron oxide nanoparticles in 465 kHz radiofrequency field. (**22**A) Exposure of 20 nm ferrous oxide nanoparticle suspension (1 mg/ml) and water to 465 kHz radiofrequency field, (**22**B) Significant increase in temperature of nanoparticles (compared to water). Nanoparticle temperature increases by 5° C. in 30 s without any increase in water temperature.

FIGS. **23**A-**23**B show confirmation of co-expression of TRPV1 and nanoparticle tether in vitro. (**23**A) Dual staining for TRPV1 and HA (upper panels). TRPV1 and biotin (middle panels) and TRPV1 and streptavidin Alexa 594 (lower panels) in transfected HEK 293t cells. (**23**B) Streptavidin coated iron oxide nanoparticle binding (10 nm) to transfected HEK 293t cells (left) and quantification in non-transfected and transfected cells (right).

FIGS. **24**A-**24**D show opening of TRPV1 channels and calcium entry in response to nanoparticle heating by RF in vitro. (**24**A) TRPV1 opening and rapid calcium entry in HEK293t cells transfected with TRPV1 and BAPTM and decorated with streptavidin coated nanoparticles in response to nanoparticle heating in RF field. Calcium entry was measured as a change in fluorescence intensity of the calcium indicator Fluo-4. (**24**B) Pseudocolored images indicating change in fluorescence intensity in TRPV1 transfected cells with RF stimulation. (**24**C) Indirect assessment of intracellular calcium via expression of luciferase under the control of a calcium dependent NFAT promoter. (**24**D) Luciferase expression is significantly increased in HEK293t cells only in the presence of all components of the NICE system: TRPV1 and the biotin acceptor protein (BAP), the addition of 20 nm iron oxide nanoparticles (NP) and the presence of 465 kHz, 110 kA/m electromagnetic field (RF).

FIGS. **25**A-**25**E show constructs for viral delivery of NICE components and RFdependent hormone release. (**25**A) Construct for constitutive expression of NICE components, BAPTM and TRPV1. (**25**B) Construct for calcium dependent expression of furin modified human insulin. (**25**C) Construct inserted into adenovirus for cre dependent expression of NICE components, BAPTM and TRPV1 using FLEX system. (**25**D) 293t cells transiently transfected with TRPV1-Baptm and NFAT insulin show a significant increase in proinsulin release with nanoparticle binding and RF exposure. (**25**E) Insulin gene expression is also significantly increased in these cells with RF exposure.

FIGS. **26**A-**26**B show combinatorial activation of transfected cells. A mixture of 2 cell populations will be studied each expressing a unique linear epitope in the first extracellular loop of TRPV1 to tether an antibody coated nanoparticle tuned to a distinct wavelength. Subsequent calcium entry increase expression of a calcium dependent luciferase unique to each cell population. (**26**A) Iron oxide nanoparticles coated with anti-His 6× antibody bind to His 6 epitope in TRPV1. Calcium entry triggers CBR luc expression. (**26**B) Gold nanoparticles coated with anti-FLAG antibody bind to FLAG epitope in TRPV1. Calcium entry triggers CBG99 luc expression.

FIGS. **27**A-**27**E show constructs for generation of transgenic mice for expression of NICE components. Transgenic mice will be generated with the insulin promoter driving expression of TRPV1 (**27**A) and BAPTM (**27**B). These mice are crossed to express both TRPV1 and BAPTM in beta cells (**27**C). An additional transgenic mouse with luciferase downstream of NFAT response elements will act as an in vivo reporter of intracellular calcium (**27**D). The resulting mice (**27**E) will express TRPV1 and BAPTM in beta cells and calcium dependent luciferase in all cells.

FIGS. **28**A-**28**F show an illustrative scheme for self-stimulation protocol with lickometer: (**28**A) a fiber connector for implant of a biocompatible 200 μm fiber optic; (**28**B) implanted fiber to deliver light to the ventral tegmental area; (**28**C) Med associates photobeam lickometer; (**28**D) the self-stimo-lick paradigm is a variation of the self-stimulation paradigm where the operant behavior is a lick. Light stimulation of ChR2 positive neurons or RF stimulation of NICE positive neurons occurs only when the mouse consumes water from the lickometer; (**28**E) animals injected with AAV-Flex-hChR2-mCherry virus (top) consume more water than controls (bottom) form the connected port. (**28**F) cumulative licks over a 2 hour trial. Light sensitive (red) and control animals (blue) in a SSL paradigm.

FIGS. **29**A-**29**G show expression of NICE constructs in Agrp and POMC neurons. (**29**A) generation of BAC transgenic mouse with His tagged TRPV1 under the control of Agrp promoter; (**29**B) transgenic mouse with Flag-tagged TRPV1 under control of POMC promoter; (**29**C) these transgenic lines are crossed to result in mice with His tagged TRPV1 expression in Agrp neurons and Flag tagged TRPV1 expression in POMC neurons of the arcuate nucleus; (**29**D) without RF stimulation neither AGrp nor POMC neurons are activated; (**29**E) in the presence of anti-His iron oxide beads and RF of 465 kHz, His-tagged Agrp neurons are activated; (**29**F) in the presence of anti-FLAG gold nanorods and RF of 13.5 MHz, FLAG tagged POMC neurons are activated; (**29**G) with both anti-His iron oxide beads and anti-FLAG gold nanorods and RF of 13.5 MHz, both His tagged Agrp neurons and FLAG tagged POMC neurons are activated.

FIGS. **30**A-**30**B. Iron oxide (IO) nanoparticles functionalized with monoclonal antibodies against the His×6 epitope tag are targeted to cells. (**30**A-**30**B) In the presence of a RF field, local heating of IO nanoparticles above the threshold for TRPV1 channel activation (42° C.) triggers calcium entry and cell activation.

FIG. **31**. Depiction of a modified TRPV1 channel as both a nanoparticle tether and effector. A short epitope tag, His×6, was introduced into the first extracellular loop of TRPV1. Modification did not significantly alter the temperature sensing ability of TRPV1.

FIG. **32**. No significant increase in proinsulin release was observed in HEK 293t cells decorated with IO nanoparticles in the presence of an RF magnetic field without TRPV1 (transfected with BAP only), in cells with TRPV1 but without nanoparticle binding (transfected with TRPV1 only), or in cells with nanoparticles and TRPV1 (TRPV1His or TRPV1 BAP) but in the absence of the RF magnetic field.

FIGS. **33**A-**33**E. In vitro studies examining the effects of RF treatment on proinsulin release and insulin gene expression replicated the findings in transfected HEK 239t cells (**33**A-**33**C). Stably transfected PC12-TRPV1His-Ins cells were injected subcutaneously into the flank of nude mice and formed tumors expressing TRPV1His (**33**D) and furin sensitive insulin constructs. Following an overnight fast, PBS or IO nanoparticles were injected into the tumors of anesthetized mice (50 ul total volume, nanoparticle concentration 8 mg/ml). Blood glucose and plasma insulin were measured before, during and after the application of an RF field (**33**E).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods and compositions for the remote control of cell function based on the use of radiofrequency waves to excite nanoparticles targeted to specific cell types. The cell type of interest expresses a temperature sensitive channel wherein excitation of the nanoparticles results in a localized temperature increase that is transduced into a cellular response. Such cellular responses, include for example, modulation of cell proliferation, cell differentiation, apoptosis, and/or activation of signal transduction pathways. In a specific embodiment of the invention, the cellular response is an increase in gene expression resulting in production of one or more physiologically active proteins. The expression of such proteins may be used to treat various inherited or acquired disorders including for example, cardiovascular disorders, central nervous system disorders, autoimmune diseases, oncological diseases, hormonal disorders, metabolic diseases, blood disorders or immune disorders. Additionally, the proteins may be expressed to treat various infectious diseases including, for example, viral, bacterial, parasitic, and fungal infections. The cellular response resulting from nanoparticle excitation may also be designed to result in an increase in gene expression resulting in production of one or more nucleic acid molecules of interest. Such nucleic acid molecules include those molecules capable of regulating protein expression, such as antisense and siRNA molecules.

The expression system of the present invention can be used with virtually any type of biological cell population, including prokaryotic and eukaryotic cells. Such eukaryotic cells include, for example, plant and mammalian cells. The specific cell type used will typically vary depending upon the type of cellular response that is sought to be regulated. For example, mammalian cells and specifically, human cells or animal cells are typically preferred for increased expression of a physiological protein for use as a therapeutic.

In an embodiment of the invention the cell type of interest is a stem cell, preferably a mammalian stem cell. For example, stem cells engineered to express NICE constructs can act as autografts to enable external control of cell function. As used herein, "stem cell" refers to any cell having the potential to differentiate into one or more different cell types, including pluripotent stem cells. Such cells include, but are not limited to, stem cells derived from a variety of different sources including, for example, bone marrow, embryonic blastocysts or yolk sac, spleen, blood, including peripheral blood and umbilical cord blood, adipose tissue and other tissues and organs. Such stem cells include, but are not limited to, hematopoietic stem cells, mesenchymal stem cells, endothelial progenitor cells or embryonic stem cells.

In a specific embodiment of the invention, the cell type of interest expresses a temperature sensitive channel wherein activation of the nanoparticles results in a localized temperature increase that is transduced into a cellular response via the temperature sensitive channel. Such temperature sensitive channels include, but are not limited to, TRPV1, TRPV2, TRPV3, TRPM8, chimeric TRP channels, and tandem pore domain potassium channels, such as TREK1, TREK2, and TASK. The localized temperature increase mediated by the excitation of the nanoparticles leads to an activation of the TRP VI channel resulting in gating of Ca2+ entry.

In a specific embodiment of the invention, the cell type of interest expresses a channel wherein activation of the nanoparticle results in motion of the nanoparticle that is transduced into a cellular response via the mechanical motion of the particle. Such motion sensitive channels include, but are not limited to, TREK-1, TRAAK, TRPV4, and TRPV1. The

localized stimulation of nanoparticle motion leads to an activation of the channel resulting in modulation of cell activity.

In an embodiment of the invention, the cells to be targeted may be genetically engineered to express one or more genes encoding physiologically active proteins of interest, such as those proteins providing a therapeutic benefit. The cells are genetically engineered in such a way that expression of the protein(s) of interest is induced in the cell upon excitation of the nanoparticles which results in a localized temperature increase or an increase in nanoparticle motion. Alternatively, the cells to be targeted may be engineered to express a non-encoding nucleic acid molecule of interest such as an antisense or siRNA molecule. Additionally, the target cells maybe genetically engineered to express a temperature sensitive protein, such as a temperature sensitive ion channel, wherein an increase in temperature mediated by the excited nanoparticles results in a cellular response through activation of the ion channel.

In another embodiment of the invention, target cells may be engineered to intracellularly express a protein that is capable of acting as an activated nanoparticle upon exposure to a RF magnetic field. Such proteins include for example, the iron storage protein ferritin. Such proteins may be expressed in the cell as fusion proteins to target their location to a specific site within the cell, for example, in close proximity to a temperature sensitive channel.

In an embodiment of the invention, recombinant expression vectors designed to express a physiologically active protein of interest, or a nucleic acid molecule of interest, such as antisense or RNAi molecules, or a protein that may act as a natural nanoparticle can be introduced into the target cells of choice.

The recombinant expression vectors, in addition to containing a nucleic acid encoding the protein or nucleic acid of interest, will contain transcriptional regulatory sequences that can be induced upon excitation of the particles resulting in expression of the protein, or nucleic acid molecule of interest. Such transcriptional regulatory sequences, include, but are not limited to, promoter and/or enhancer sequences that induce gene expression in response to ion channel activation. Such regulatory sequences include, but are not limited to the calcium response elements, referred to herein as SRE, CRE and NFAT RE.

The cells may be genetically engineered using techniques well known in the art. Such techniques include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, for example, the techniques described in Sambrook J et al. 2000. Molecular Cloning: A Laboratory Manual (Third Edition), and Ausubel et al (**1996**) Current Protocols in Molecular Biology John Wiley and Sons Inc., USA). Any of the methods available in the art for gene delivery into a host cell can be used according to the present invention to deliver genes into the target cell population. Such methods include electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. In a specific embodiment, a viral vector that contains a nucleic acid encoding the protein or nucleic acid of interest and a transcriptional regulatory sequence that can be induced upon excitation of the nanoparticles can be used. Such viral vectors include for example, retroviral, adenoviral or adeno-associated viral vectors. (See, Kozarsky and Wilson, 1993, Current Opinion in Genetics and Development 3:499-503 for a review of adenovirus-based gene delivery).

For general reviews of the methods of gene delivery see Strauss, M. and Barranger, J. A., 1997, Concepts in Gene Therapy, by Walter de Gruyter & Co., Berlin; Goldspiel et al, 1993, Clinical Pharmacy 12:488-505; Wu and Wu, 1991, Biotherapy 3:87-95; Tolstoshev, 1993, Ann. Rev. Pharmacol. Toxicol. 33:573-596; Mulligan, 1993, Science 260:926-932; and Morgan and Anderson, 1993, Ann. Rev. Biochem. 62: 191-217; 1993, TIBTECH 11(5): 155-215.

In order to access different organs non-invasively, it is necessary to have an electromagnetic field that is capable of passing through tissue as part of a system that allows some cells to be activated while the majority are not. Accordingly, radiofrequency (RF) electromagnetic fields are used for this purpose. RF signals at low and medium frequencies penetrate tissues freely and without significant energy absorption making it now possible to adapt this system for in vivo use (Jokela International Union of Radio Science 2008). In contrast to tissues, metallic/metal oxide nanoparticles placed in an alternating RF field absorb energy and heat in a controlled manner depending on the strength of the field, a process known as induction heating (Fortin et al., J. Am, Chem. Soc. 129:2628-2635). The heating capacity depends on nanoparticle composition, size, perhaps shape and the frequency and power of the RF field and, as such, it is possible to regulate the heat generated within the physiological temperature range.

In vitro, the temperature response achieved is fast and decays quickly (inverse of the square of the distance) thus providing a rapid, functional 'on-off' switch. The nanoparticles employed, for example, magnetic iron oxide and gold spheres, are easily prepared, have little or no intrinsic cell toxicity and can readily be adapted to target cells by incorporating streptavidin, antibodies, or pharmacological agents (Samanta B. et al. J Mater Chem 18: 1204-1208; Wang A Z. et al. 2008 Expert Opin Biol Ther 8: 1063-1070). Therefore, they are well suited for inducing localized temperature changes that can be transduced into cellular responses in vitro and in vivo.

Nanoparticles of differing compositions and shapes are heated at defined rates by different electromagnetic field frequencies and strengths. Nanoparticles for use in the present invention include, but are not limited to, metallic nanoparticles, and metal oxide nanoparticles. Such nanoparticles include, but are not limited to, iron oxide nanoparticles, gold nanoparticles, and the like. For example, iron oxide nanoparticles are maximally heated by an EM frequency of around 465 kHz while gold nanoparticles heat at an EM frequency of 13.5 MHz, with the field strength determining the rate of heating. This property potentially allows distinct EM frequencies to differentially heat nanoparticles of different compositions and/or shapes. Nanoparticles consisting of different chemistries, such as, but not limited to, gold and iron oxide, and of different shapes, particularly nanoparticles of different aspect ratios (e.g., spheres vs. rods), can be chosen based on their discrete heating frequencies and resistivities. The described invention provides non-limiting, illustrative compositions and methods encompassing different chemistries and spheres of specific sizes. The nanoparticles can be directed to distinct cell populations via cell-specific expression of unique tethers and then, using RF generators and tunable amplifiers with a range of excitation frequencies, excite different cell populations alone or in combination.

Further, the nanoparticles can be conjugated to various biological or chemical moieties that bind a specific receptor or target a specific cell type. In such instances, the nanoparticles may be externally applied to the cells. The ligand can comprise a small molecule, peptide, antibody, nucleic acid, protein, carbohydrate, lipid, polyethylene glycol

derivatives or any combination thereof. Metal nanoparticles can readily be functionalized to target define cell populations by coating with specific antibodies that recognize proteins that are normally expressed on a cell or transfected into that cell (Samanta et al., J. Nat. Chem. 18: 1204-1208; Wang et al, Expert. Opin. Biol. Ther. 8: 1063-1070). For example, streptavidin, which binds to biotin with extremely high affinity, may be conjugated to nanoparticles. Through conjugation of streptavidin to nanoparticles, a system is provided whereby streptavidin-conjugated nanoparticles can be coupled to biotin-labeled cells through the streptavidin/biotin high-affinity reaction. Loading of nanoparticles onto the cells permits targeting of heat to said cells.

In addition to external application of nanoparticles to the target cell of interest, cells may be genetically engineered to express proteins which can act as naturally occurring nanoparticles and which can be activated by a RF magnetic field. Such proteins include, for example, the iron storage protein ferritin, the bacterial gene MagA, ceruloplasmin and transferrin.

The method of the present invention comprises contacting a target cell population with nanoparticles for a time sufficient to permit binding of the nanoparticle to the surface of the target cell. In an embodiment of the invention, the nanoparticles are administered in vivo to a subject resulting in contacting of a target cell population with nanoparticles for a time sufficient to permit binding of the nanoparticle to the surface of the target cell.

In an embodiment of the invention, the target cells are cultured, using routine tissue culture methods well known to those of skill in the art. Cells are then washed with a buffer, such as a phosphate-buffered saline (PBS) and a solution of nanoparticles is added to the target cells. In an embodiment of the invention, the nanoparticle solution comprises a mixture of the tissue culture media in which the cells are cultured and nanoparticles. Cells are incubated with the nanoparticles for a time sufficient to permit efficient binding of the nanoparticles to the target cells. Transfer of nanoparticles to the target cells can be monitored using, for example, flow cytometry.

In a preferred embodiment of the invention the target cell population are stem cells. Also within the scope of the invention are nanoparticle labeled cells that have been genetically engineered to express a desired protein, or nucleic acid of interest. For example, nanoparticle labeled cells may be engineered to express proteins capable of providing a therapeutic benefit.

The present invention further provides pharmaceutical compositions comprising nanoparticles, nanoparticle-labeled cells and/or cells that express nanoparticles intracellularly and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known to those skilled in the art and include, but are not limited to, 0.01-0.1M and preferably 0.05M phosphate buffer, phosphate-buffered saline (PBS), or 0.9% saline. Such carriers also include aqueous or non-aqueous solutions, suspensions, and emulsions. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, saline and buffered media. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Preservatives and other additives, such as, for example, antimicrobials, antioxidants and chelating agents may also be included with all the above carriers.

Nanoparticle-labeled cells and/or cells that express nanoparticles intracellularly can also be incorporated or embedded within scaffolds which are recipient-compatible and which degrade into products which are not harmful to the recipient. These scaffolds provide support and protection for nanoparticle-labeled cells that are to be transplanted into the recipient subjects.

The present invention provides methods and compositions which may be used to provide a therapeutic benefit for treatment of various diseases. Specifically, through the use of nanoparticle-labeled cells and/or cells that express nanoparticles intracellularly, a therapeutic protein, or nucleic acid molecule of interest, may be delivered to a subject in need of treatment through administration of nanoparticle labeled cells. Alternatively, nanoparticles themselves may be administered to a subject in need of treatment, wherein said nanoparticles are targeted to endogenous cells of the subject wherein excitation of the nanoparticle results in a localized temperature increase that is transduced into a cellular response.

Various delivery systems are known and can be used to administer the nanoparticles, nanoparticle labeled cells and/or cells that express nanoparticles intracellularly. Such compositions may be formulated in any conventional manner using one or more physiologically acceptable carriers optionally comprising excipients and auxiliaries. Proper formulation is dependent upon the route of administration chosen.

The methods of the invention, comprise administration of nanoparticles and/or nanoparticle labeled cells and/or cells that intracellularly express a nanoparticle, in a pharmaceutically acceptable carrier, for treatment of various disorders or diseases. "Administering" shall mean delivering in a manner which is effected or performed using any of the various methods and delivery systems known to those skilled in the art. Administering can be performed, for example, pericardially, intracardially, subepicardially, transendocardially, via implant, via catheter, intracoronarily, intravenously, intramuscularly, subcutaneously, parenterally, topically, orally, transmucosally, transdermally, intradermally, intraperitoneally, intrathecally, intralymphatically, intralesionally, epidurally, or by in vivo electroporation. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carvers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a therapeutically effective amount of the therapeutic compound, preferably in purified form, together with a suitable amount of carrier so

as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

The appropriate concentration of the compositions of the invention which will be effective in the treatment of a particular disorder or disease will depend on the nature of the disorder or disease, and can be determined by one of skill in the art using standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses maybe extrapolated from dose response curves derived from in vitro or animal model test systems. Additionally, the administration of the compound could be combined with other known efficacious drugs if the in vitro and in vivo studies indicate a synergistic or additive therapeutic effect when administered in combination.

Additionally, the progress of the recipient receiving the treatment may be determined using assays that are designed to detect the physiologically active protein expressed by the nanoparticle targeted cells.

The present invention further relates to transgenic non-human animals that may be engineered to contain cells that respond to nanoparticle excitation in a desired fashion. For example the transgenic animals may be engineered to express cell surface receptors that act as binding partners for the nanoparticles. Said target cells may either naturally, or through genetic engineering, express a protein, or nucleic acid molecule of interest upon nanoparticle excitation. Alternatively, the transgenic animals may be engineered to intracellulary express a nanoparticle, such as for example a naturally occurring iron nanoparticle. Such transgenic animals provide in vivo model systems for studying normal physiological processes as well as disease processes. The transgenic animals of the invention may further be useful as in vivo model systems for use in identification and testing of novel therapeutic compounds of interest.

According to one aspect of the described invention, the method of the invention can be implemented as follows. First, expression of both a biotin acceptor protein (BAP) fused to the transmembrane domain of platelet derived growth factor receptor (PDGFR) as a tether for streptavidin coated nanoparticles, and TRPV1, a temperature sensitive cation channel can be expressed in specific cells using specific promoters. Second, cells are "decorated" by delivering streptavidin-coated iron oxide nanoparticles into the region where the BAP is expressed. The high affinity of streptavidin and biotin results in the cells being coated with the metallic/metal oxide nanoparticles. Studies in vitro have confirmed this to be the case. Third, the cultured cells, or an animal, are exposed to a RF field of defined strength at an intensity that will increase the local temperature of the nanoparticle decorated cells, activate the TRPV1 channel and thus triggering calcium influx.

In some embodiments, the system can be modified such that only one construct is used for both tethering of the nanoparticle and gating of Ca2+ entry. For example, the TRPV1 protein may be engineered as a fusion protein capable of direct tethering of the nanoparticle. In an embodiment of the invention, the TRPV1 protein may be engineered as a fusion protein containing any "tag" that does not interfere with the functioning of the channel. Such tags are well know to those of skill in the art. As described in detail below, the TRPV1 protein can be expressed as a fusion protein containing HIS tags. In such a case, the nanoparticles are coated with anti-HIS antibodies for targeting to the cell.

The present invention provides methods and compositions for studying the role of different cell types in a complex organism. The definitive test of cell function is to selectively turn on or off the activity of a single cell type in a living animal and examine the effect on physiological function. The present invention provides for the use of nanoparticles to activate defined cell populations remotely with radiowaves. According to another embodiment, ferrous oxide coated with streptavidin can be used to decorate cells, which express a biotin acceptor protein under the control of cell specific promoters. These same cells are engineered to also express TRPV1, a single component, temperature-sensitive ion channel that can detect small changes in temperature within the physiological range and by conformational change allow graded calcium entry. Exposing the metal coated cells to a defined electromagnetic field increases the local temperature and activates TRPV1 channels resulting in a Ca2+ current and cell activation. Data is provided below that confirms the efficacy of this method both in vivo and in vitro. The technology can be used to modulate functions such as hormone release and neural activity. A means is also provided for combinatorial activation of different cells using a modified TRPV1 and nanoparticles fabricated from other metals that can be excited at different wavelengths. This tool can be used, for example, to examine the roles of specific peripheral and CNS cell populations in energy metabolism.

The methods and compositions of the invention can be used to refine the methodology by decorating different cell types with distinct particles tuned to different wavelengths to activate ensembles of different cell populations in various combinations. Further, the ability of NICE to modify hormone release to regulate glucose metabolism in diabetic animals in vivo can be further refined. The methods and compositions can also be used for stimulation of action potentials in electrically excitable cells to modify behavior and can be used to study the role of specific hypothalamic populations in (NPY and POMC) control of appetite.

Example 1. Radio-Wave Regulation of Plasma Glucose in Mice

The present invention provides methods and compositions to remotely and selectively switch on the activity of a single cell in a living organism and examine the effects on physiological function using nanoparticle induced cell excitation (NICE). The technique targets temperature sensitive calcium channels (TRPV1) to defined cells. These cells are decorated with metal nanoparticles which are heated by an external radiofrequency field. This in turn opens the TRP channel to stimulate calcium influx. Calcium entry initiates downstream events such as depolarization (neurons), hormone release (endocrine cells) or gene expression.

The studies described herein demonstrate the efficacy of NICE at stimulating calcium influx, modulating hormone release and stimulating gene expression both in vivo and vitro.

Material and Methods

Nanoparticles. Iron oxide nanoparticles (10-50 nm diameter), functionalized with a surface carboxylic acid group, were purchased from Ocean Nanotech (Springdale, Ark.). The nanoparticles were conjugated to either mouse monoclonal anti-His antibody (AbD Serotec, Raleigh, N.C.) or streptavidin (Jackson Immunoresearch Laboratories, West

Grove, Pa.) using carbodiimide and N-hydroxysuccinimide activation technique as employed by magnetic nanocrystal conjugation kit (Ocean Nanotech). Heating studies were performed using 1 ml of a bulk solution (1 mg/ml) of nanoparticles dispersed in water placed in an eppendorf inside the solenoid and the temperature of the suspension was monitored using a fiber optic system (Luxtron, Lambda photometries, Herts, UK).

RF magnetic-field. A 465 kHz sinusoidal signal was provided by a signal generator and applied through an amplifier (both Ultraflex, Ronkonkoma, N.Y.) to a 2-turn solenoid coil with a radius of 2.5 cm to produce a magnetic field strength of 5 mT. Samples were placed within the solenoid. A 13.56 Mhz sinusoidal signal was provided by a signal generator (RF Instrumentation, PA) and applied through an amplifier (Comdel, Gloucester, Mass.) to a 2-tum solenoid coil with a radius of 2.5 cm).

Plasmids. TRPV1 On pcDNA3.1) was a kind gift of Wolfgang Liedkte (Duke University, NC) and cloned into pEGFP-N1 (Clontech, Mountainview, Calif.). It was modified by PCR (Fast start PCR, Roche) to introduce His×6. Nuclear factor of activated t-cells (NFAT) response elements and minimal promoter were from pGL4.30[luc 2P/NFAT-RE/Hygro (Promega, Madison, Wis.). Serum response element (SRE), cyclic AMP response element (CRE) and form modified human insulin sequences were synthesized by Integrated DNA technologies (Coralville, IO). The calcium dependent response elements—SRE, CRE and NFAT response elements were each used in triplicate. The use of these three response elements increased the likelihood that at least one such mechanism would be active with high sensitivity in all of the cell types that we engineered. They were also used to achieve high specificity since each of these elements is reported to respond only to repeated or sustained changes in intracellular calcium. BAPTM, the transmembrane domain of platelet derived growth factor receptor fused to an extracellular biotin acceptor protein, was a kind gift of Dr. B Tannous, Massachusetts General Hospital, MA). $TRPV1^{His}$ and calcium responsive form insulin were cloned into MSCV-hygro and MSCV-puro plasmids (Clontech,) respectively for retrovirus production using Phoenix packaging cells. Mouse ferritin heavy chain was obtained from ATTC (Manassas, Va.) in pCMV sport6 and mouse ferritin light chain 1 was obtained from Invitrogen (Carlsbad, Calif.) in pYX-Asc. These were cloned downstream of EF1 alpha promoter in pCR2.1 with a flexible linker region to create ferritin light chain—linker—heavy chain fusion protein. The fidelity of PCR products was confirmed by DNA sequencing.

Cell culture and in vitro studies. Human embryonic kidney cells (HEK 293T) were cultured in Dulbecco's modified eagle medium with 10% fetal bovine serum (Gibco, Carlsbad, Calif.) at 37° C. and 5% CO_2. PC12 cells were cultured in RPMI medium 1640 with 10%) horse serum and 5% fetal bovine serum (Gibco) at 37° C. and 5% CO_2. Phoenix ecotropic packaging cells (Stanford University) were grown in Dulbecco's modified eagle medium with 10%>fetal bovine serum (Gibco) at 37° C. and 5% CO_2.

Stable cell lines were produced by retroviral infection of PC12 cells using the Phoenix system. Briefly, Phoenix eco cells (2×10^6 cells per 6-cm dish) were transfected with MSCV-puro or hygro plasmids as described above. After 24 hours, the medium was replaced and the cells placed at 32° C. Medium was aspirated after a further 24 h and spun to remove cell debris. The Phoenix cell supernatant was added to PC12 cells (plated at 1×10^6 cells per 6-cm dish) using a 1:2 dilution in RPMI medium/10% FBS with polybrene (4 μg/ml, Sigma-Aldrich, St Louis, Mo.). Cells were incubated at 32° C. for a further 24 h before replacing the medium with RPMI/10% FBS. Selection medium was added 48 h after infection.

Embryonic stem cells were electroporated with a calcium dependent human insulin plasmid and selected with puromycin for 3 weeks. Resistant cells were identified for insulin insertion by Southern blot analysis before electroporation with $TRPV1^{His}$ plasmid and selection with hygromycin for 3 weeks. Three double resistant clones were screen by quantitative PCR for expression of insulin and TRPV1 and by immunohistochemistry for expression of TRPV1 and His tag. The ES clone with high expression by qPCR and IHC was used for RF studies. Cells were plated onto gelatin coated 12 mm cover glass (without feeder cells) for 96 hrs before assessing RF dependent release of calcium dependent human insulin.

For immunocytochemistry and RF studies, cells were cultured on 12-mm cover glass (Fisher Scientific, Pittsburgh, Pa.) coated with collagen (BD biosciences, Bedford, Mass.) and poly-D-lysine (Millipore, Billerica, Mass.). For EM studies, cells were cultured in 3 cm dishes. Cells were transfected 24 h after plating using lipofectamine 2000 (Invitrogen, Carlsbad, Calif.). For temperature dependent studies, cells were plated in 24-well plates coated with collagen and poly-D-lysine and transfected 24 h later. Culture medium was replaced 18 h after transfection and holotransferrin (2 mg/ml, Sigma) was added to cells transfected with ferritin. Cells were studied 72 h after transfection.

Temperature dependent release of calcium dependent human insulin: 24 h prior to the study, cells were placed in serum free medium at 32° C. to ensure minimal activation of TRPV1 and calcium dependent pathways. On the day of study, cells were preincubated for 30 min in 500 μl phosphate buffered saline (PBS) before incubation in 250 μl of calcium imaging buffer (Caterina et al. 1997 Nature 389: 816) at 32 or 44° C. for 1 h. At the end of 1 h, the supernatant was aspirated, spun to remove cell debris and frozen at −80° C. until assay. Studies were performed in quadruplicate on three occasions.

RF dependent release of calcium dependent human insulin: 24 h prior to the study, cells were placed in serum free medium at 32° C. to ensure minimal activation of TRPV1 and calcium dependent pathways. On the day of study, cells were preincubated for 30 min in 500 μl PBS or 500 μl of functionalized iron oxide nanoparticles (1 mg/ml) resuspended in PBS. Cells were washed three times in PBS before incubation in 300 μl of calcium imaging buffer at room temperature (control) or in a RF field at room temperature. The supernatant was removed at 15, 30, 45 or 60 min depending on the study, spun to remove cell debris and frozen at −80° C. until assay. For gene expression analysis, cells from the supernatant and cover glass were lysed and the lysate stored at 80° C. until RNA purification. For apoptosis studies, the cells were incubated with functionalized nanoparticles at 1, 2, 4 or 8 mg/ml before RF treatment and immunocytochemistry. For RF dependent time course from stable PC12 cells, cells were left in serum containing medium prior to treatment to more accurately replicate conditions in vivo before performing the studies as described above. Medium was removed for assay at 15 and 30 mins.

For studies examining the role of TRP channels in RF mediated proinsulin release, ruthenium red (100 μM) was added to the calcium imaging buffer. For studies to examine the role of calcineurin in the activation of calcium dependent

insulin gene, Tacrolimus (100 nM, Tocris Bioscience, Minneapolis, Minn.) was added to the medium for 24 hours prior to RF treatment. To examine if the effects of RF heating on iron oxide nanoparticles were confined to decorated cells, 3-cm dishes of HEK 293T cells were transfected with either BAPTM or TRPV1 and calcium dependent human insulin. After 24 h, the two transfected cell populations were trypsinized and mixed to form a co-culture with adjacent cells expressing BAPTM and TRPV1/human insulin.

Calcium Imaging. Transfected cells were washed three times in PBS then loaded with Fluo-4 3 μM (Invitrogen) in the presence of sulfinpyrazone 500 μM (Sigma) for 60 min at room temperature. Cells were washed again in PBS then incubated for 30 min either with functionalized nanoparticles with sulfinpyrazone or in sulfinpyrazone in PBS. Cells were washed and then imaged in calcium imaging buffer. Imaging was performed using a Deltavision personal DV imaging system (Applied Precision, Issawaq, Wash.) equipped with a custom-made ceramic lens. Cells were imaged before and during RF treatment or before and after treatment with 200 μM 2 aminoethoxydiphenyl borate (2-APB).

Immunocytochemistry, Immunohistochemistry and Electron Microscopy. Immunocytochemistry (ICC) was used to detect and quantify apoptotic cells following RF field treatment. Two assays were employed, TUNEL assay visualized using Apoptag Fluorescein direct in situ apoptosis detection kit (Millipore) and ICC for activated caspase-3 (Promega). After RF treatment, cells were washed twice in PBS and then fixed for 15 min in 2% paraformaldehyde (Electron Microscopy Services, Hatfield, Pa.). Cells were then stained according to the manufacturers' protocols. Expression of NFAT1 was also examined using ICC. Control or RF treated transfected cells were washed and fixed as above then incubated in for 1 h in blocking buffer (3% BSA (Sigma) and 2% goat serum (Sigma) in PBS with 0.1% Triton-X (Sigma)). Following blocking cells were incubated in primary antibody, rabbit anti-NFAT1 (Cell signaling), 1:50, diluted in blocking buffer overnight at 4 degrees. Cells were then washed three times in PBS before incubation in secondary antibody (goat anti-rabbit 488 1:1000) diluted in blocking buffer for 1 h. The cells were then washed a further three times in PBS before inverting and mounting using Fluoromount with DAPI (Southern Biotech, Birmingham, Ala.).

ICC was also used to examine expression of ferritin fusion. Cells were washed twice with PBS, fixed and blocked as above. Cells were incubated in primary antibody, rabbit anti-ferritin light chain (Dako, Carpinteria, Calif.), 1:1000, diluted in blocking buffer for 1 h. Cells were washed three times in PBS before incubation in secondary antibody (goat anti-rabbit 488 1:1000) diluted in blocking buffer for 1 h. The cells were washed a further three times in PBS before inverting and mounting using Fluoromount (Southern Biotech, Birmingham, Ala.).

Immunohistochemistry (IHC) was used to confirm expression of TRPV1 and His and quantify apoptotic cells in tumors. Tumors were fixed in 10% formalin (Sigma) at 4° C. overnight then placed in 30% sucrose in PBS at 4° C. for a further 24 h. Tissue was embedded in OCT and frozen before 20 μm cryosections were cut and placed directly on glass slides. Slides were placed at 55° C. for 1 h then stored at −80° C. before staining. Apoptag Fluorescein direct in situ apoptosis detection and IHC for activated caspase-3 were performed according to the manufacturers' instructions. Staining for TRPV1 and His was performed as follows. Slides were washed three times with PBS then incubated in blocking buffer for 2 h followed by overnight incubation at 4° C. with primary antibody diluted in blocking buffer (rabbit anti-TRPV1 1:500, mouse anti-His 1:1000 (Sigma)). Slides were washed 3-times in PBS and then incubated overnight at 4° C. with secondary antibody diluted in blocking buffer (goat anti-rabbit 488 and goat anti-mouse 594 both at 1:1000). Slides were washed 3-times in PBS before applying Fluoromount and a coverglass (Fisher Scientific).

Images were acquired using a Zeiss Axioplane microscope and captured digitally with separate band-pass filters using the multichannel module of the Axio Vision Zeiss software. Additional images were acquired using confocal microscopy (LSM 510 laser scanning confocal microscope; Carl Zeiss Microimaging, Inc.). Quantification of TUNEL and active caspase-3 immunostaining was performed by an investigator blinded to the treatment group.

Electron microscopy was used to quantify nanoparticle binding to the cell membrane and to image ferritin in transfected cells. Cells were fixed in 2% paraformaldehyde/2.5% glutaraldehyde/0.1M cacodylate buffer, pH 7.4, for 15 minutes before pelleting and further fixation for 1 h. Cells were then treated with 1% osmium tetroxide (1 h, on ice) and 0.5% uranyl acetate (1 h) before dehydration with graded ethanol and treatment with propylene oxide (2×15 min). The cells were infiltrated with 50% EPON epoxy resin (Miller-Stephenson, Sylmar, Calif.) and 50%>propylene oxide overnight then 100% EPON (2×2 h) before curing at 60° C. for 2 days. Blocks were cut with a diamond knife on a Leica UltracutE (Buffalo Grove, Ill.) and ultra-thin (~70 nm) sections were collected on uncoated 200 mesh grids and stained with uranium and lead. Grids were viewed with a Tecnai SpiritBT Transmission Electron Microscope (FEI, Hillsboro, Oreg.) at 80 KV and pictures were taken with Gatan 895 ULTRASCAN Digital Camera (Pleasanton, Calif.).

ImmunoEM was used to confirm binding of nanoparticles to TRPV1. HEK 293T cells were seeded on Aclar (Ted Pella Inc, Redding, Calif.) in 24 well plates and transfected with TRPV1His 24 hours later. 72 hours after transfection, cells were washed twice with PBS and incubated with anti-His coated iron oxide nanoparticles for 30 mins. Following two further PBS washes, cells were fixed in a fixative containing fresh 4.0% paraformaldehyde and 0.1 M sodium cacodylate buffer (pH 7.4) for overnight. Cells were processed for immunoelectron microscopy: after incubating with a blocking solution containing 3% BSA and 0.05% saponin in sodium cacodylate buffer for 20 min, the primary antibody was applied and incubated for overnight at 4° C.; in the following day, after extensive wash secondary antibody conjugated with nanogold (Nanoprobes, Inc. Yaphank, N.Y.) (1:50) was applied and incubated for 2 hours; subsequently, with series of wash, silver enhancement was conducted by using silver enhancement kit (Nanoprobes, Inc. Yaphank, N.Y.). Cells were re-fixed with 2.5% glutaraldehyde in the cacodylate buffer, lightly postfixed with 1% osmium tetraoxide (10 min), dehydrated by a graded series of ethanol, infiltrated with EMBed812 resin and embedded in the same resin. Ultra-thin sections were cut and examined in the electron microscope (100CX JEOL, Tokyo, Japan) with the digital imaging system (XR41-C, Advantage Microscopy Technology Corp, Danver, Mass.). Control experiment was done by following the same procedure except for the step of omitting primary antibody and applying the blocking solution, instead.

Animals and In vivo studies. Male athymic NCr-nu/nu mice (NCI-Frederick, 6 weeks old), an outbred strain, were

used and housed under controlled light conditions (12 h light/12 h dark) and temperature (22° C.), single-caged, and fed ad libitum on standard mouse chow. Animal care and experimental procedures were performed with the approval of the Animal Care and Use Committee of Rockefeller University (protocol 11421) under established guidelines.

To generate subcutaneous tumors, 5×10^6 $^{PC}12$ cells stably expressing $TRPV1^{His}$ and calcium dependent human insulin or calcium dependent human insulin alone were re-suspended in a 1:1 mixture of PBS and growth-factor reduced Matrigel (BD biosciences) and injected into the flank of anesthetized mice bilaterally. Radio frequency studies were performed 4 weeks later. Blood glucose was monitored weekly. Mice were fasted overnight before all studies.

Study 1: Mice with $TRPV1^{His}$ insulin xenografts (n=7) were anesthetized with inhaled isoflurane. PBS or iron oxide nanoparticles functionalized with anti-His antibody were injected into the tumor (5×10 μl). After 30 min, mice were treated with an RF magnetic field for 30 min by placing in a solenoid connected to the RF generator. Tail vein samples were taken at −30 and 0 min before RF magnetic field treatment and at 10, 20, 30, 45, 60, 90 and 120 min after the onset of RF treatment. Retro-orbital blood was taken using EDTA coated capillary tubes at −30 and 30 min for plasma insulin measurement. As the mice are outbred and had high inter-individual variability in blood glucose, the studies were performed with a cross-over design with each mouse receiving first PBS and then one week later receiving nanoparticle injections. Nanoparticle injections could not be performed first because the particles remain within the tissue for prolonged periods (Giustini et al, 2011 Nanotechnology 22:345101).

Study 2: Mice with $TRPV1^{His}$ insulin xenografts (n=6/group) were anesthetized and were randomized to receive either functionalized iron oxide nanoparticles or PBS. An identical treatment protocol to study 1 was used and intra-tumoral temperature and core body temperature were monitored using a fiber optic temperature monitoring system. Thermal imaging using FLIR infrared camera SC325 (North Billerica, Mass.) was performed on a subset of mice. After 120 min, the mice were sacrificed and the tumors removed. Each tumor was divided in two and one half snap frozen in liquid nitrogen for RNA extraction and the one half placed in 10% formalin for immunohistochemistry.

Study 3: Mice injected with PC12 cells stably expressing calcium dependent human insulin (n=8) were used and study 1 repeated.

Study 4: Mice injected with PC12 cells expressing calcium dependent human insulin were used (n=6/group) and study 2 repeated.

Study 5: Mice injected with PC12 cells expressing $TRPV1^{His}$ and calcium dependent human insulin were used (n=6/group) and study 1 was repeated using nanoparticles which had not been conjugated to anti-His antibody.

Study 6: Mice injected with PC12 cells expressing $TRPV1^{His}$ and calcium dependent human insulin were used (n=7/group). Study 1 was repeated with mice injected initially with PBS and treated with RF. Blood glucose and insulin were measured as described above. One week later, mice were injected with anti-His conjugated nanoparticles and treated with RF. Blood glucose was monitored as above. After a further week, mice received a second injection of anti-His conjugated nanoparticles, were treated with RF and blood glucose and insulin were measured.

Assays. Proinsulin was measured in cell supernatants by ELISA (Alpco, Salem, N.H.) according to manufacturer's protocol. Blood glucose was determined using a Breeze 2 glucometer (Bayer; Leverkusen, Germany). Blood was spun for 10 min and plasma was collected. Plasma levels of human insulin, produced by xenografts, were determined in mouse plasma by human specific ELISA (Alpco).

Real-Time PCR. Total RNA was isolated by homogenizing tissue in TRIzol reagent (Invitrogen) or cells in buffer RLT and purifying the RNA using QIAGEN RNA prep kit. Complimentary DNA was synthesized using QIAGEN omniscript RT kit. Realtime PCR was performed using the TaqMan system (Applied Biosystems; Foster City, Calif.) according to the manufacturer's protocol.

Statistics. All data were analyzed for statistical significance using the Student's t test. P values are as indicated.

Nanoparticle Characterization. Iron oxide nanoparticles purchased from Ocean Nanotech (Catalog # SHP-20-50) were further characterized. The particles were coated with oleic acid and a proprietary polymeric coating, which is carboxy-terminated for further functionalization. The particles were specified to be 20 nm in diameter with a standard deviation of <5%. This was confirmed in the current work; TEM analysis of the size distribution yielded an average diameter of 19.8±2.7 nm (FIG. **3**B). The particles were estimated to have a 4 nm oleic acid/polymeric coating in addition to the nanoparticle diameter observed in TEM. X-ray photoelectron spectroscopy (XPS) allowed identification of all elements within ~5 nm of the nanoparticle surface, as well as a more precise investigation of the nanoparticle surface chemistry and iron oxide content. XPS characterization (FIG. **3**C) of the IONP indicated only the presence of iron, oxygen and carbon as would be expected from the polymeric coating. The shoulder in the Cls peak is consistent with the presence of carboxyl groups, as indicated in FIG. **3**D. Moreover, the structure of the iron oxide particles was indicated by Ocean Nanotech to be magnetite (Fe_3O_4) for this particle size. However, magnetite and maghemite (γ-Fe_2O_3) is difficult to distinguish using x-ray diffraction (XRD) due to similarities in crystal structure. Indeed, comparison with JCPDS files #39-1346 (maghemite) and #75-0033 (magnetite) indicates that the current iron oxide particles are likely a mixture of both crystallographic structures.

Studies were also performed to extend the analysis of the heating characteristics of the nanoparticles at different frequencies. A limited number of frequencies are suitable for medical use in addition to the 465 kHz used previously. The heating of particles using a frequency of 13.56 Mhz which is the lowest of the remaining available frequencies and therefore the least likely to result in non-specific adsorption was also tested. The power level chosen was the maximum level that did not result in significant heating of water (200 W) in the absence of nanoparticles. At 465 kHz, observed a rapid increase in temperature for a suspension of 20 nm iron oxide nanoparticles with a temperature increase of 17° C. that reached a plateau at 300 s. A smaller rise in temperature (6° C.) was seen with 25 nm particles with only minimal heating for larger sizes of iron oxide nanoparticle. In contrast, at 13.56 MHz, there was significant heating for a broader range of particle sizes (10-25 nm) with greatest heating observed for 15 nm particles (11° C.) and very little heating of 20 nm particles, with only a maximum temperature rise of 2° C. However, the heating rate for 15 nm particles was lower than that for 20 nm particles at 465 kHz and did not plateau over the test period. The heating of 25 nm particles was similar at both frequencies.

Nanoparticle heating. Temperature decay from the iron oxide nanoparticle (IONP) surface has been explored (Rast and Harrison, 2010 Nanotech Conference and Expo 2010,

Anaheim, Calif., June 21-24, p. 910-914; Hergt et al, 2010 IEEE Trans. Mag. 34:3745; Wilson O. et al, 2002 Phys. Rev. B 66:224301; Jordan et al, 1993 Int. J. Hyperthermia 25:499) and is complicated by factors such as the heat capacity of the surrounding medium, the nanoparticle ligand coating, and diffusion away from the nanoparticle surface. The change in temperature in the vicinity of the nanoparticle decreases as the inverse of the radius, and may be approximated by the conductive heat transfer equation (Fourier's Law) (Rabin, 2002 Int. J. Hyperthermia 18: 194):

$$\Delta T = \frac{V_{np}Q}{4\pi k}\frac{1}{r} = \frac{q\rho D^2}{12k}$$

where V_{np} is the nanoparticle volume, Q is the total dissipated heat, r is the nanoparticle radius, q is the heating rate (W g^{-1}), ρ is the nanoparticle density, D is the diameter of the heated volume, and k is the thermal conductivity of water (0.64 W m^{-1}° $C.^{-1}$). Though it has been calculated that heating sufficient to trigger channel activation cannot be achieved on the single nanoparticle scale (AT~10^{-5}° C./particle), it has been shown that accumulating a significant number of iron oxide nanoparticles in a small volume may raise the temperature sufficiently to have an effect. In a separate study, thermoresponsive polymer coatings on iron oxide nanoparticles have demonstrated increased drug release in radiofrequency fields, indicating that heating at the nanoparticle surface affected the structure of the thermopolymer and drug release profile. Both calculations and experiments in the literature have confirmed that ~1.2 mg of IONP are required to raise the temperature of a 1 cm^3 region by 5° C. (Derfus et al, 2007 Adv. Mater. 19:3932). Based on this published literature and assuming a cell volume of 9.05×10^{-10} ml, we would require 1.1×10^{-9} mg/cell (ie 1.1 pg/cell) to give a nanoparticle density of 1.2 mg/ml to cause a local 5° C. increase in temperature. From EM images, we observe an average of 2×10^5 nanoparticles/cm. Assuming the particles are evenly distributed, this would give 4×10^{10} nanoparticles/cm^2. For a 20 μm cell, the surface area is 1.25×10^{-5} cm^2 (assuming a sphere) and therefore the calculated number of nanoparticles decorating the cell is 5×10^5 nanoparticles. The density of Fe_3O_4 is 5.24 g/cm^3, and each nanoparticle is 20 nm in diameter, giving a nanoparticle weight of 1.75×10^{-16} g. Therefore, to achieve 1.1 picograms of nanoparticles per cell one would need at least 6.26×10^3 nanoparticles. Thus it is calculated that an almost 100 fold greater nanoparticle decoration than that required to achieve a 5° C. local increase in temperature has been obtained.

Results

A system has been developed that allows remote activation of protein production by engineered cells in vitro and in vivo. The method (FIG. **1**) uses iron oxide nanoparticles (FeNPs) that are coated with antibodies against His (anti-His) and that bind a modified TRPV1 channel with an extracellular His×6 epitope tag ($TRPV1^{His}$). As disclosed herein RF treatment, local heating of bound anti-His FeNPs activates the temperature-sensitive TRPV1, resulting in a calcium current to activate a Ca^{2+}-sensitive promoter placed upstream of a modified human insulin reporter gene.

FeNPs was used for the following reasons: They heat at 465 kHz, a relatively low frequency that minimizes tissue heating; particles of 20 nM or less diffuse in the extracellular space (Wang et al., 2008 Expert Opin. Biol. Ther. 8: 1063; Deflaco et al. 2001 Science 291:2608; Thorne et al, 2006 Proc. Natl. Acd. Sci USA 103:5567); and these particles can be derivatized with antibodies. At 465 kHz (5 mT), substantial heating was observed for 20- and 25-nm FeNP suspensions (FIGS. **2**A-**2**E). A 20-nm FeNP suspension had an initial heating rate of 0.15° C./s and a specific absorption rate (SAR) of 0.63 W/g, whereas the SAR of water at this field frequency and strength was less than 0.004 W/g. As shown by electron microscopy, a His-tag insertion into the first extracellular loop of TRPV1 provided a site for significant and specific FeNP binding (FIGS. **3**A-**3**D) with direct heat transfer to the adjacent channel (FIG. **4**). Human embryonic kidney (HEK) 293T cells expressing $TRPV1^{His}$ and decorated with 20 nM FeNPs conjugated to anti-His showed a significant increase in intracellular Ca^{2+} after 10 s of RF exposure (FIG. **3**D).

Calcium entry was next used to induce gene expression via a novel synthetic 5' regulatory region composed of three Ca^{2+} response elements in cis: serum response element (SRE), cyclic adenosine monophosphate response element (CRE), and nuclear factor of activated T cell response element (NFAT RE) (Hardingham et al. 1999 Microsc. Res. Tech. 46:348; Rao 2009 Nat. Immunol. 10:3) with a minimal promoter. This was placed upstream of a modified human proinsulin gene with furin cleavage sites replacing beta-cell-specific convertase cleavage sites to allow insulin processing in non-beta cells (Shirin et al, 2001 Gene Ther. 8: 1480) (FIG. **5**A).

HEK 293T cells expressing the Ca^{2+}-dependent human insulin construct and $TRPV1^{His}$ were incubated with functionalized FeNPs. RF treatment of the FeNP-decorated cells resulted in a significant increase in proinsulin release (RF-treated 671±235% (SEM) basal versus 100±13.9% for controls, $P<0.02$) and insulin gene expression (RF-treated 2.20±0.53 insulin gene expression relative to basal versus 1.0±0.18 for controls, $P<0.05$). These were blocked by the TRP channel inhibitor, ruthenium red (FIG. **6**A). There was a trend toward an increase in proinsulin release after 15 min of RF treatment (likely through release of a small pool of preformed insulin-containing vesicles), with significant proinsulin release at 1 hour when insulin gene expression had also significantly increased (FIG. **6**B). Control studies confirmed that proinsulin release required all system components (i.e., TRPV1, nanoparticles, and RF magnetic field) and that RF-dependent insulin secretion was confined to FeNP-decorated cells (FIGS. **5**B-**5**C). RF treatment induced NFAT translocation into the nucleus, and RF-dependent proinsulin release was blocked by a calcineurin inhibitor, tacrolimus (FIGS. **5**D-**5**E). RF treatment of cells incubated with FeNPs (1 to 8 mg/ml) did not induce apoptosis as assessed by immunohistochemistry for active caspase 3 (Tewaari et al, 1995 Cell 81:801)) and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling (TUNEL) (Gavrieli et al 1992 J. Cell Biol. 119:493) (FIGS. **5**F-**5**G). It was also shown that RF could stimulate proinsulin release from mouse embryonic stem cells expressing $TRPV1^{His}$ and the Ca^{2+}-dependent human insulin construct (FIGS. **7**A-**7**D).

Next, a comparison was made of the single-component system to a multicomponent system previously reported (Huang et al., 2010 Nat. Nanotechnol. 5:602) and composed of (i) a membrane-tethered biotin acceptor protein, (ii) a bacterial biotin ligase to biotinylate this protein to enable binding of (iii) streptavidin-coated nanoparticles, and (iv) a wild-type TRPV1 as the effector. Although this system induced Ca^{2+} entry in vitro and activated endogenous temperature sensing of *Caenorhabditis elegans* neurons, the

complete system was not tested in vivo because the exogenous TRPV1 channel was not used in this prior study. It was found that the single-component system had denser nanoparticle binding, faster calcium entry, and a trend toward more robust proinsulin release (FIGS. **8**A-**8**G). These attributes led to the testing of the single-component $TRPV1^{His}$ system in vivo in mice by using xenografts of engineered neuroendocrine PC12 cells, which robustly secrete peptides via the regulated pathway for protein secretion.

Exposure of a PC-12 cell line stably expressing $TRPV1^{His}$ and the calcium-dependent human insulin construct (PC12-$TRPV1^{His}$-Ins) to RF after FeNP application significantly increased proinsulin release and insulin gene expression in vitro (FIGS. **9**A-**9**D). The PC12-$TRPV1^{His}$-Ins cells were injected subcutaneously into the flank of nude mice to form tumors (FIG. **9**F). There was no change in plasma glucose with tumor growth (FIG. **9**E). Phosphate-buffered saline (PBS) or FeNP (50-μl total volume, nanoparticle concentration of 8 mg/ml) were injected into the tumors of fasted mice, and blood glucose and plasma insulin were measured before, during, and after RF application (see FIG. **11** A for protocol). RF treatment resulted in a significant decrease in blood glucose in nanoparticle-treated PC12-$TRPV1^{His}$-Ins tumor mice (FIG. **10**A) (The change in blood glucose at 30 min for FeNP-treated was −53.6±8.90 mg/dl, versus PBS-treated, −11.0±9.72 mg/dl; $P<0.005$. At 45 min, the change in blood glucose for FeNP-treated mice was −60.9±11.6 mg/dl versus PBS-treated −9.74±8.52 mg/dl; $P<0.005$. At 60 min, the change in blood glucose for FeNP-treated mice was −55.1±13.2 mg/dl versus PBS-treated, −6.24±15.3 mg/dl; $P<0.0001$). There was also a highly significant difference in the cumulative change in blood glucose (area under the curve, AUC) between PBS-treated and FeNP-treated PC12-$TRPV1^{His}$-Ins tumor mice over the course of the study (FIG. **10**B) [AUC (0 to 120 min) for PBS-treated was 272±692 mg/dl min versus FeNP-treated, −2695±858.3 mg/dl min; $P<0.002$]. Plasma insulin was significantly increased after RF treatment in FeNP-treated but not PBS-injected mice (Figure IOC) [plasma insulin for FeNP-treated (−30 min) was 2.26±0.76 μI-U/ml (where 1 μI-U/ml=0.006 pmol/L) versus FeNP-treated (30 min), 3.25±0.64 μl-U/ml; $P<0.05$. PBS-treated (−30 min) was 1.83±0.38 μI-U/ml versus PBS-treated (30 min), 1.75±0.36 μI-U/ml]. Lastly, insulin gene expression was significantly increased in RF-treated, FeNP-injected tumors (FIG. **10**D) (relative insulin gene expression in FeNP-treated, no RF samples was 1.0±0.2 versus FeNP-treated with RF, 2.0±0.3, $P<0.05$) without increasing c-fos expression (FIG. **11**B). Core temperature did not change significantly with RF exposure, and the intratumoral temperatures (23° to 31° C.) remained well below the 42° C. threshold of TRPV1, indicating that cell activation is due to localized, cell surface-specific gating of TRPV1. There was no difference in apoptosis between FeNP-injected tumors in the presence or absence of the RF magnetic field (FIGS. **11**C-**11**D). A significant decrease in blood glucose was also seen with serial FeNP injection and RF treatment (FIGS. **11**E-**11**F). To confirm that the effects on blood glucose were not due to nonspecific insulin release via thermal effects of nanoparticles on the tumor, the in vivo study was repeated, first in mice injected with PC12 cells expressing the Ca^{2+}-dependent human insulin construct but not $TRPV1^{His}$ and then in mice with tumors expressing $TRPV1^{His}$ and insulin but injected with nanoparticles without anti-His conjugation. There was no significant effect on blood glucose in either study after PBS or FeNP injection and RF treatment despite similar intratumoral temperatures (FIGS. **12**A-**12**D).

The above approach requires direct application of nanoparticles to TRPV1 expressing cells by incubation (in vitro) or injection (in vivo). An alternative is to engineer cells to synthesize nanoparticles intracellularly. For this purpose, the iron storage protein ferritin was chosen, which forms a naturally occurring iron nanoparticle (Farrant, 1954 Biochim. Biophys. Aca 13:569; Sana et al., 2010 Biointerphases 5:FA48) (FIG. **13** A, FIGS. **14**A-**14**B). Ferritin has been stably overexpressed in mice for over 2 years without evident pathology (Ziv et al., 2010 NMR Biomed 23:523). A fusion peptide of ferritin light chain, flexible linker region, and ferritin heavy chain fixes the ratio of light to heavy chains and increases iron binding (Iordanova et al., 2010 J. Biol. Inorg. Chem. 15:957). Transfecting cells with ferritin fusion protein resulted in 12.6±2.86 ferritin particles per 0.2 μm^2 with an average distance to the cell membrane of 60.3±2.85 nm (FIG. **14**B). RF treatment of cells expressing the ferritin fusion protein, TRPV1, and Ca^{2+}-dependent human insulin significantly increased proinsulin release (RF treated, 457±103% basal versus control, 100±14.9%) basal; $P<0.005$) and insulin gene expression (relative insulin gene expression for RF treated, 1.58±0.19 versus control, 1.0±0.17; $P<0.05$) (FIG. **13**B). Intracellularly generated FeNPs were roughly two-thirds as effective in stimulating proinsulin release as exogenous FeNP. In the absence of TRPV1, insulin secretion and gene expression were unchanged in ferritin-expressing cells. Thus, ferritin expression may provide a genetically encoded source of nanoparticles for RF-mediated cell activation.

As disclosed herein both externally applied and endogenously synthesized nanoparticles can be heated by radio waves to remotely activate insulin gene expression and secretion. RF-mediated cell activation does not require a permanent implant, and the cells to be activated can be localized (when using exogenous nanoparticles) or dispersed (by using genetically encoded nanoparticles). Genetically encoded ferritin nanoparticles may also provide a continuous source of nanoparticles for cell activation.

The use of an epitope-tagged TRPV1 with antibody-coated nanoparticles resulted in high nanoparticle density in proximity to the channel and could gate calcium in response to power levels of a 465-kHz RF field that are within Food and Drug Administration guidelines (Halperin et al, 2008 Proceedings of the 2008 IEEE Symposium on Security and Privacy Oakland Calif. May 18-21, 2008 p. 129-142). The use of a single construct for particle binding and calcium entry also simplifies DNA delivery using viral vectors or other approaches (Nathwani et al, 2011 N. Engl. J. Med. 365:2357). Additionally, an epitope-tagged channel offers the choice of activating distinct cell populations in the same organism with different RFs to selectively and independently heat nanoparticles bound to cell specific tags. For endogenous particles, mutations of ferritin that alter the metal it encapsulates could enable combinatorial cell activation (Butts et al., 2008 Bichemistry 47: 12729).

A noninvasive, nonpharmacological means has been developed for cell stimulation and validated it in vitro and in vivo. This system provides a useful tool for basic research and represents an initial step toward noninvasive regulation of protein production for possible therapeutic purposes. This approach could be used to treat protein deficiencies by providing regulated expression of proteins that are difficult to synthesize or to deliver [such as central nervous system (CNS) replacement of hexosaminidase A for Tay-Sachs] or to allow CNS delivery of recombinant antibodies to treat brain metastases. This approach could also enable the acti-

vation of other Ca^{2+}-dependent processes, such as muscle contraction or firing of action potentials.

Example 2. Nanoparticle Induced Cell Excitation

Effects of NICE in Vivo. Data is provided herein which shows the effectiveness of NICE in vivo. For these studies the effect of NICE on insulin release was examined in implanted cells. Stably transfected PC12 cells expressing TRPV1, a nanoparticle tether and insulin driven by a calcium dependent promoter (NFAT-insulin) were implanted into nude mice to form subcutaneous tumors. In a cross-over design, either vehicle (PBS, 5×10 ul) or functionalized nanoparticles (20 nm, 5×10 ul) were injected into each tumor (n=8 mice). Thirty minutes after injection, mice were exposed to a radio frequency field (RF) for a period of 30 minutes. Blood glucose and insulin were monitored and the tumors harvested at the end of the study period. This protocol is described visually in FIG. **20**A. Mice receiving nanoparticle injection and RF showed a significant reduction in blood glucose, a significant increase in circulating insulin and a significant increase in tumor expression of insulin (FIGS. **20**B-**20**E). There was no difference in apoptosis between groups based on immunohistochemical assessment of TUNEL or activated caspase-3.

The results demonstrate the usefulness of NICE as a tool for non-invasive stimulation of cell function in vivo. Additional studies can be performed to examine the effect of stimulating endogenous cell populations using transgenic mice expressing a nanoparticle tether and TRPV1, with or without calcium dependent gene expression. It is also possible to examine the effects of stimulating cell populations derived from individual-specific induced pluripotent stem cells (iPSC) injected into immune-competent mice. Viral free iPSC populations can be reprogrammed to a wide variety of tissues and also modified to express NICE components. These cell populations would allow the non-invasive study of specific stimulation of defined cell types and/or defined genes within these cells providing a valuable tool in the investigation of cell function particularly as it pertains to complex behaviors.

Intracellular Nanoparticle Synthesis. In its present form, NICE technology requires external nanoparticle application by incubation (in vitro) or injection (in vivo). For peripheral tissues, this may be achieved by intravenous administration but modulation of neuronal activity requires intracerebral administration. This is advantageous in some situations where stimulation of an anatomically defined subpopulation of a dispersed neural group is needed. However, a variation of the existing NICE technology with intracellular nanoparticle synthesis using chimeric ferritin proteins targeted to an intracellularly tagged TRPV1 channel is being studied.

The iron storage protein, ferritin, is a complex of heavy and light chains that is capable of binding 4500 ferric ions or picograms of iron per cell. This iron binding capacity has allowed ferritin to be utilized as an MRI contrast agent in many studies. Two chimeric ferritin peptides have been developed, one fused at the N-terminal to Egfp and one fused to a highly stable, high affinity (subnanomolar) camelid anti-gfp antibody known as a nanobody (FIG. **21**A). These adaptations allow adjacent ferritin complexes to bind to form ferritin aggregates and EM images show these are of the order of 40-50 nm diameter (FIG. **21**B). In addition, the temperature dependent calcium channel, TPRV1, is modified by attaching the nanobody sequence to its intracellular N-terminal which then tethers the ferritin aggregate. This brings the heating component (ferritin bound iron) and the effector component (TRPV1) of NICE together at the cell surface.

There are 4 forms of the ferritin complex that have been tested-ferritin light chain-linker-heavy chain (ferritin complex) expressing in the cytoplasm, ferritin complex expressed at the cell membrane, ferritin complex with egfp fusion that binds to TRPV1 with anti-gfp camelid antibody fusion and the system described above. FIG. **15** demonstrates proinsulin release from 293T cells transfected with calcium dependent insulin and either TRPV1/myristoylated ferritin, camelid anti-GFP fused to TRPV1/EGFP ferritin or camelid anti-GFP fused to TRPV1/EGFP ferritin/camelid anti-GFP fused to ferritin in response to RF treatment.

Example 3. Nice: Iron Oxide Nanoparticles

Iron oxide nanoparticles, functionalized with streptavidin to decorate the cells have been used for several reasons. Firstly, the streptavidin-biotin complex is the highest affinity non-covalent bond known and directs the nanoparticles stably to the cell surface. Secondly, the heat generated by nanoparticles in an RF field depends on both Brownian motion and Neel fluctuation, the internal rotation of the magnetic moment. When nanoparticles are bound to the cell surface, the proportion of heat generated by Brownian motion is significantly decreased. In contrast to other particles, such as cobalt ferrite nanoparticles, heat generated by iron oxide particles is primarily through Neel fluctuation rather than Brownian motion (Fortin et al., 2007 J. Am. Chem Soc. 129:2628-2635). Thirdly, functionalized iron oxide nanoparticles are readily available in a number of sizes allowing the heating response to be tuned through field strength and frequency, and particle size. The size of particles that diffuse freely in a number of in vitro and in vivo settings has been defined and 20-30 nm beads have been found to be optimal.

Using an alternating magnetic field (465 kHz, 110 kA/m) provided by a commercial induction generator (Ultraflex Power Technologies) and a custom-made, water cooled, induction coil (4.5 cm diameter), it has been demonstrated that the temperature of a suspension of iron oxide nanoparticles increases when it is exposed to the appropriate RF frequency. While much lower temperature increases are necessary for NICE in vitro or in vivo, an increase of up to 17° C. can be achieved when a suspension of 20 nm iron oxide particles (1 mg/ml) are exposed to a 465 kHz, 110 kA/m field (FIGS. **22**A-**22**B). It has been noted that a 5° C. rise in nanoparticle temperature is sufficient to open TRPV1 channels and can be reached in approximately 30 s with no increase in water temperature.

Iron oxide nanoparticles coated with streptavidin were used to decorate specific cell populations by expression of a tether in the form of a biotin acceptor protein (BAP) fused to the transmembrane domain of PDGFR and tagged with hemagglutinin (HA) (Tannous et al, 2006 Nat Methods 3:391-396) The biotin acceptor protein is modified by endogenous biotin ligase. The affinity of streptavidin and biotin is 10-15M and this high affinity has been shown by us to lead to specific binding of the nanoparticles only to cells that express the BAP tether. It has been shown that nanoparticles can decorate transfected HEK293t cells that express an HA tagged BAPTM fusion protein (FIGS. **23**A-**23**B). Electron microscopy confirms that streptavidin-coated ferrous oxide nanoparticles bind to the cell membrane and quantification reveals that this is significantly greater on cells transfected with the BAPTM fusion protein versus cells

not expressing this construct. In addition, immunocytochemistry demonstrates significant co-localization of TRPV1 with HA (BAP) immunoreactivity, TRPV1 with biotin immunoreactivity, and TRPV1 with Alexa 594-streptavidin binding. These results confirm that constructs can drive co-expression of TRPV1 and the BAPTM fusion protein in the same cells (FIGS. **23**A-**23**B).

With NICE, the local temperature change achieved by heating nanoparticle-coated cells is transduced into calcium entry by targeted expression of TRPV1 channel. This is a single component channel that detects small changes in temperature just above the physiological range (>42° C.) as a result of a conformational change allowing calcium entry (Caterina et al., Nature 389:816-824). The response is proportional to the temperature change and relatively rapid, thus transducing temperature variations induced by the heated nanoparticles into a graded calcium current with attendant cell activation. Repeated heating also potentiates calcium entry, i.e., there is no desensitization. Generally, ion channels such as TRPV1 offer many advantages for modifying cell activity, including as described above, their fast temporal resolution and the ability to target their expression genetically without the tissue damage often seen with direct electrical stimulation. In this respect the activation of a temperature sensitive channel provides the same advantages as the reported light activated cation channel but without the need for an indwelling catheter, and with the potential, by using different nanoparticles, to effect activation of different cell types in response to different RF frequencies to modulate multiple cells in the same local region.

It has been confirmed that NICE can induce calcium entry in response to radio waves using streptavidin-coated iron oxide nanoparticles, expression of a cell surface biotin acceptor protein and the temperature sensitive TRPV1 channel in transfected HEK293t cells both with calcium imaging and a calcium sensitive NFAT-luciferase reporter construct as the readout (FIGS. **24**A-**24**D). The calcium response can be modulated both by the power of the RF field and by the exposure time. These findings confirm the feasibility of the method in vitro. The methodology in vivo in vertebrates has been applied and validated. It is important to note that implementing the non-invasive, induction heating of nanoparticles in an RF field poses several technical challenges that have been addressed in the studies performed to date and that these will also need to be taken into account in in vivo studies. The RF field heats not only metallic/metal oxide nanoparticles but also the metal components of any structure within the field. Therefore, the apparatus to be used for imaging, recording and behavioral monitoring must be designed so as to remove any metal components and replace them with ones that are inert in an RF field. Nonetheless, the design and optimization of the custom equipment required to implement this technique is feasible.

In summary, a combination of nanoparticle heating in an RF field and a temperature responsive ion channel was used to convert localized temperature changes into remote, temporally controlled, and anatomically defined activation of specific cells. The NICE technology can further studied in vitro and in vivo using two classical physiological processes requiring specific calcium dependent functions: hormone release and neural activation. This technique can be applied in vivo to develop a novel method to regulate glucose metabolism and to examine the contribution of specific neural populations to feeding.

Example 4. Analysis of Nice In Vitro

The use of NICE in vitro can be extended as follows: (i) examining the cellular responses to nanoparticles over time, (ii) validating the ability of NICE to stimulate hormone release in vitro, (iii) modulating neural activity in vitro, in hippocampal neurons or (iv) dopaminergic neurons in brain slices and (v) examining the combinatorial activation of distinct cell populations using a novel combination of epitope-tagged TRPV1 channel and functionalized nanoparticles tuned to heat at distinct frequencies.

Cellular Responses to Nanoparticles and NICE. Nanoparticles to be used in these studies will be prepared using well described methods and optimized to reduce nonspecific binding by use of hydrophobic particles and functionalization with polyethylene glycol. Iron oxide nanoparticles will be synthesized using iron (III) acetylacetonate, reduced in the presence of oleylamine and oleic acid to yield monodispersed and single crystalline Fe_3O_4 nanoparticles with a high magnetic moment (Xu Zea 2009 Chem Mater 21: 1778-1780 The resulting hydrophobic nanoparticles then are functionalized with carboxyl-terminated polyethylene glycol (PEG-COOH), which will further covalent attachment of targeted biomolecules (streptavidin or antibodies) through EDC/NHS chemistry and reduce nonspecific uptake by cells (Xie Jea 2007 Adv Mater 19:3163-3166) Gold nanoparticles will be prepared by a seed-mediated growth synthesis (Sau T, Murphy C 2004 Langmuir 20:6414-6420, with the shaping surfactant hexadecyltrimethylammonium bromide replaced with thiolated PEG-COOH through an extensive aqueous-organic ligand exchange process. Wijaya A 2008 Langmuir 24:9966-9969). Ligand exchange will be confirmed through Fourier transform IR analysis and zeta potential measurements. Nanoparticle characterization will take place through transmission electron microscopy (TEM), dynamic light scattering, X-ray diffraction and, in the case of gold, surface plasmon resonance to ensure monodispersity and stability.

NICE utilizes cell surface tethering of nanoparticles for cell specificity and to provide proximity for TRPV1 channel activation. The fate of the nanoparticles after binding will be examined using both quantitative and qualitative tools by inductively coupled plasma mass spectrometer (ICP-MS) and microscopy, respectively. HEK 293t cells transfected with TRPV1 and BAPTM will be incubated with the nanoparticles and, at 5 min, 30 min, 2 h, 4 h, 12 h and 24 h the cells will be washed with Tween 20 to remove surface-attached nanoparticles. This supernatant as well as the homogenized cells will then be dissolved in aqua regia and analyzed using ICP-MS. These experiments will give a detailed time-course of nanoparticle uptake over time. Localization and integrity of the nanoparticles also will be investigated using TEM and confocal microscopy. Transfected HEK 293t cells will be incubated with nanoparticles and at various times (as above), cells will be fixed and embedded. Cell sections (50-70 nm) will be stained with uranyl acetate and TEM analysis will be used to identify the location of nanoparticles within the section, using the high contrast of electron dense iron and gold, as well as further identification with electron-dispersive spectroscopy (EDS). Confocal micrographs also can be used to determine the location of nanoparticles at the surface and within cells, using fluorescently labeled streptavidin conjugated to iron oxide particles or the dark-field light scattering of gold nanoparticles.

Initial studies indicate that NICE does not lead to apoptosis in NICE excited or non-transfected cells. However, more detailed studies of cell viability following nanoparticle binding and RF exposure will be conducted on HEK 293t cells transfected with TRPV1 and BAPTM, incubated with nanoparticles before and following RF excitation. Mitochondrial function will be examined using the standard MTT

assay Absorbance will be read at 590 nm to quantify the mitochondrial reduction of yellow MTT to purple formazan. Membrane integrity following nanoparticle binding and RF exposure will be assessed by colorimetric measurement of lacatate dehydrogenase activity released from damaged cells. The effects of the NICE protocol on DNA damage also will be examined using an in situ apoptosis detection system Zoppi N et al. 2008 Biochim Biophys Acta 1783: 1177-1188). Quantitative PCR (qPCR) will also be performed on RNA extracted from transfected HEK 293t cells, with and without RF exposure, for markers of the Unfolded Protein Response (including C/EBP homologous protein, phosphorylated inositol-requiring enzyme 1 alpha, eukaryotic initiation factor 2 alpha and activating transcription factor 3)(2-4)(2-4)(2-4)(2-4) need which are characteristic of ER stressKyriakakis et al. 2010 Cell Signal 22: 1308-1316; Winnay et al. 2010 Nat Med 16:438-445; Gjymishka A, et al. 2009 Biochem J 417:695-703

The effects of nanoparticle uptake by cells on the ability to activate TRPV1 and induce calcium entry also will be examined. Cells transfected with TRPV1 and BAPTM will be incubated with nanoparticles for increasing lengths of time, based on the studies above, such that initial time points demonstrate minimal NP uptake while later time points can include cells with intracellular nanoparticles. Cells will be loaded with the calcium indicator, Fluo-4, and calcium entry in response to the RF field will be measured. Further studies will examine the effect of NICE on neighboring cells by preparing two populations of transfected cells, one expressing BAPTM and binding Alexa 350-streptavidin iron oxide nanoparticles and one expressing TRPV1 and the fluorescent marker, mCherry. These cell populations will be mixed and loaded with Fluo-4 before calcium imaging in the presence of the RF field. Absence of calcium entry in cells expressing TRPV1 and mCherry would indicate that heating of nanoparticles bound to one cell does not affect adjacent cell.

Effect of NICE on Hormone Release From Cultured Cells In Vitro. A classical calcium dependent process is hormone release from endocrine cells. The ability of NICE system to induce changes in hormone release in vitro using stably transfected cell lines has tested. Constitutive expression was achieved using a CMV promoter to drive TRPV1 channel expression and a beta actin promoter to drive BAPTM expression (FIG. **25**A). Insulin expression will be controlled by the Ca2+ sensitive NFAT promoter as described herein. Expression of TRPV1 and BAP will be confirmed by immunocytochemistry (IHC). See FIGS. **8**A-**8**G.

The ability of NICE to modify endogenous insulin gene expression, synthesis and release will first be assessed using the RIN m5F insulinoma cell line expressing TRPV1-BAPTM in vitro. On the day of study, the stably transfected cells will be incubated in Kreb's phosphate buffer (KRB) containing streptavidin coated 20 nm iron oxide nanoparticles for 30 min. Nanoparticle decorated cells will be exposed to the 465 kHz RF field and the effects will be assessed after 5 min, 10 min, 30 min and 2 h, in part guided by the time course studies described above. Additional studies will examine the effect of repeated pulsed RF exposure for 5, 10 or 20 min periods for a total period of 2 h. These results will guide the RF intervals used for combinatorial studies. Calcium imaging will be used to determine the time course of calcium entry and calcium induced insulin release into the media will be measured by ELISA with insulin gene expression examined by qPCR. The effects of RF field strength and duration on insulin secretion will be examined. Control studies will examine the effect of TRPV1 and BAPTM expression on insulin secretion in the absence of RF stimulation and the effects of RF stimulation without addition of nanoparticles.

Calcium influx into cells can regulate gene expression via calcium dependent response elements. To assess the ability of NICE to modify gene expression, cells are engineered to express and release insulin in a Ca2+ dependent manner. As above, insulin is expressed downstream of a promoter with multiple Nuclear Factor of activated T-cell (NFAT) response elements and a minimal TATA promoter which has been shown to result in a significant increase in expression in response to raised intracellular calcium. This NFAT-TATA promoter is used to drive a bicistronic construct with modified human insulin and luciferase expression (FIG. **1**). Processing of proinsulin to insulin relies on two beta-cell specific prohormone convertases, so a modified human proinsulin with engineered furin cleavage sites is used as this is processed to mature insulin in non beta-cells both in vitro and in vivo (Shifrin A L, et al. 2001 Gene Ther 8: 1480-1489) its release can be differentiated from endogenous murine insulin release in vivo. This construct is stably transfected into PC12 cells already expressing $TRPV1^{His}$ to generate PC12-NICE-Ins cells. Studies demonstrate these cells secrete mature insulin. See FIGS. **9**A-**9**F.

The ability of NICE to induce insulin expression and release is studied. Cells are incubated with streptavidin iron oxide nanoparticles for the final 30 min of the preincubation period. The cells are then washed and placed in a 465 kHz RF field and the effects on insulin expression and release are examined by qPCR and ELISA, respectively. The effects of RF field strength and duration on gene expression and insulin release are examined and optimized. Studies in HEK 293T cells transiently transfected with TRPV1-BAPTM orTRPV1 and NFAT insulin confirm the ability of NICE to induce insulin gene expression and hormone release. See FIGS. **8**A-**8**G and FIGS. **6**A-**6**B, respectively.

Effect of NICE on Electrically Excitable Cells In Vitro. Calcium entry into electrically excitable cells induces depolarization and initiates action potentials. NICE will be used to regulate the activity of electrically excitable neurons in culture and in tissue slices in vitro. The ability of NICE to induce neural activity will be examined in primary hippocampal cell cultures. These cells will be infected with recombinant adenovirus expressing TRPV1-BAPTM constructs and then incubated with streptavidin-coated nanoparticles. Nanoparticle decorated cells will be exposed to the RF field and the effects assessed by calcium imaging and whole cell patch clamping. Preliminary studies indicate electrophysiological recording in the electromagnetic field is feasible. These studies will provide details of the intracellular calcium concentration achieved, the temporal resolution of the calcium entry in neurons, the degree of depolarization and spike activity achieved with NICE, and the effects of multiple RF exposures. Currents induced by RF activation will be measured while holding the neurons in voltage clamp. Membrane depolarization and spikes will be determined in current clamped neurons to determine the kinetics of activation and precision of control. Additional control experiments will examine the effect of TRPV1 and BAPTM expression on electrical properties of neurons in the absence of RF stimulation, the effects of RF stimulation without nanoparticle binding and to determine if there is a bystander effect in cells adjacent to those decorated with nanoparticles. In addition, the strength of the RF will be titrated to find the minimum field strength required for inducing an action potential.

Assays of the Effects of NICE in Brain Slices Ex Vivo. The ideal neuronal activation strategy provides anatomical specificity that, for the NICE system, would require expression of TRPV1 and BAPTM in a defined neural population. A recombinant adenovirus expressing a Flip-excision construct (Atasoy D, et al. 2008 J Neurosci 28:7025-7030) will be used to achieve cre-dependent expression of TRPV1 and BAPTM (Ad-FLEX-NICE) (FIG. **25** C). In this construct, in the absence of cre recombinase, TRPV1 and the beta actin promoter will be in an inverted orientation and inactive. In the presence of cre, TRPV1 and the beta actin promoter return to the correct orientation and are locked in place by the excision of the additional lox site. This system will allow cell specific expression of the TRPV1 and BAPTM in cells that express cre with little or no expression in cells that do not express cre. Transgenic mice expressing cre recombinase in dopamine transporter neurons (DAT-cre) will be crossed to a reporter strain, ROSA26-lox-stop-lox-EYFP mice (Ekstrand M I, et al. 2007 Proc Natl Acad Sci USA 104: 1325-1330) DAT-cre/YFP mice (age 4 weeks) will receive a stereotactic injection of high-titer Ad-FLEX-NICE stocks (~150 nl of stock of 108 infectious units) into the ventral tegmental area (VTA). In a subset of animals, expression of the construct will be determined by triple IHC to confirm co-localization of YFP (expressed solely in cre neurons), TRPV1 and Alexa-streptavidin binding. Wild-type mice also will be injected to ensure there is no expression of the cre dependent construct in the absence of cre recombinase. Ten to 14 days after viral delivery, mice will be sacrificed and sections (200 μm) will be cut. After resting, slices will be incubated with streptavidin-coated iron oxide nanoparticles for 30 min. The electrophysiological properties of infected, decorated neurons will be determined by patch clamp recording in the absence and presence of RF stimulation. Overall, these studies will confirm the ability of NICE to stimulate Ca2+ influx and neural activity in neural slices in vitro.

Combinatorial Activation of Specific Cellular Populations. The NICE system will be refined further to allow combinatorial activation of specific multiple cell populations, even if they are interspersed, using epitope tagged TRPV1 channels. Nanoparticles of different compositions and shapes heat at different EM power and frequency with different rates. For example, iron oxide nanoparticles are heated by a frequency of 465 kHz which does not heat gold, whilst gold nanoparticles heat rapidly at a frequency of 13.5 MHz. Furthermore the response characteristics of the particles also are influenced by their size. Thus, gold could be activated at a much lower RF field strength than iron oxide (i.e., gold heating faster than iron oxide) (Saleh S. et al. J. Biomedical Science and Engineering, 2008, 1, 182-189) Hence, even in the presence of both gold and iron oxide nanoparticles it is possible to selectively activate gold. Uniquely modifying TRPV1 channels expressed under the control of cell-specific promoters, provide distinct cell surface tags to direct nanoparticle binding. Particles can be specifically targeted to different cell types by coating them with recombinant antibodies directed against short epitopes. This can allow differential regulation of distinct cell populations in the same anatomical region. Specific antibodies recognizing a library of short linear epitopes that have been identified using phage display will be used. These epitopes will be inserted in frame into the first extracellular loop of TRPV1 which has been shown can be modified without altering the response characteristics of this channel.

Two different nanoparticles will be targeted: iron oxide (465 kHz) and gold nanoparticles (13.5 MHz) (Moran C, et al. 2009 Nano Research 2:400-405) to two different cell populations (FIGS. **26**A-**26**B). Carboxyl-terminated nanoparticles will be functionalized with recombinant single chain Fv antibody fragments (scFv) (Vigor K L et al. 2009 Biomaterials) to the specific short linear epitopes, His6× (6aa) and FLAG (8aa). Constructs will be generated in which these epitopes are introduced into the 1st extracellular loop of the TRPV1 channel. As mentioned above, it has been shown that this does not interfere with the temperature sensing properties of the channel. Each construct will be transfected into HEK 293t cells and paired with a distinct NFAT-RE driven luciferase reporter (CBRluc-red luciferase, CBG99luc-green luciferase) to give two different reporter read-outs of calcium entry for each cell type. Post-transfection, the two cell lines will be mixed and cultured together for a further 48 h before incubating in serum free medium overnight. On the day of study, the cells will be incubated with a cocktail of two nanoparticles; iron oxide functionalized with anti-His6× and gold nanoparticles functionalized with anti-FLAG. The localization of different particles to different cells will be confirmed using IHC. The cells will then be exposed to sequential pulses (5 min, 10 min or 20 min) of RF frequencies of 465 kHz and 13.5 MHz using a variable frequency amplifier for a total of 40 minutes at each frequency before the cells are lysed and individual luciferase activity measured.

These studies will make use of existing nanoparticle technology but nanoparticles of differing chemistries (e.g., iron oxide and gold), size (5-50 nm), and shape (spheres, rods) also will be developed to produce a range of distinct RF excitation profiles and power-heating profiles to improve this combinatorial approach. These in vitro studies provide evidence that the technology is able to activate ensembles of two or more different classes of cells or neurons alone or in combination even if these cells are colocalized in a small anatomical region.

Example 4. In Vivo Studies of Nice on Hormone Release

The goal of an artificial endocrine organ has yet to be achieved but the ability to remotely control hormone expression and release can provide a significant advance towards this aim. Once the effects of NICE on insulin synthesis and release have been optimized in vitro, in vivo studies to examine the effects of NICE on insulin release will be carried out.

The power required to create an RF field increases with the square of the coil diameter and thus a significantly more powerful generator (50-75 kW) will be required for these in vivo studies as compared to those required in vitro. Generators with sufficient power are readily commercially available (Ultraflex Power Technologies, NY). The size of the behavioral chamber will be kept to a minimum to reduce the power required whilst ensuring the mouse is able to move freely. Studies will focus on the design of both the coil and the plexiglass chamber used for assessment to ensure a uniform RF field is achieved. Modifications of the coil and generator will be made pending the results of these studies.

Effect of NICE on Insulin Expression in Implanted Cells In Vivo. Initial studies will examine the ability of NICE to regulate calcium dependent modified insulin expression in vivo as an indication of whether NICE can be employed to regulate gene expression and hormone release. Stably transfected PC12-NICE-Ins cells expressing TRPV1, BAPTM, and NFAT driven modified insulin will be used since these cells can synthesize and secrete insulin and are capable of

forming subcutaneous tumors in immunodeficient mice (Fritz M D et al. 2006 Exp Cell Res 312:3287-3297). These stably transfected cells will be injected subcutaneously into nude mice to create tumors expressing TRPV1, BAPTM, and NFAT-insulin IRES luciferase constructs. This will be confirmed by IHC. Freely diffusable iron oxide nanoparticles (20 nm) or vehicle will be injected into the tumor and the effects of RF stimulation on blood glucose and insulin, and glucose tolerance will be examined. Insulin expression will be determined by qPCR of tumor RNA in a subset of mice. Luciferase expression, as an indicator of calcium entry, in tumors will be confirmed by luminometer studies in vivo (Birsoy K. et al, 2008 Proc Natl Acad Sci USA 105: 12985-12990). Further studies will focus on the effect of stimulating PC12-NICE-Ins cells on glycemic control and glucose tolerance in streptozocin-treated diabetic nude mice. Initial studies, based on in vitro studies described above, will optimize the time period of RF exposure, by examining these measures after 5, 10, 20 or 40 mins of RF exposure. Insulin and glucose levels will be measured immediately following RF stimulation and at 10 min, 30 min, 1 h and 2 h thereafter to follow the time course of the insulin response to stimulation. In this, and all in vivo studies, a number of mice will be examined in detail post-mortem for pathological changes that may be associated with nanoparticle administration or RF exposure.

Effect of NICE on Endogenous Insulin Release In Vivo. For studies examining the effect of NICE on endogenous insulin release, transgenic mice will be used to express the NICE components. Two transgenic mouse lines will be generated to overcome the lower expression of the second gene after an IRES. The first will use an insulin promoter to drive TRPV1 expression (FIG. **27** A) and the second will use the insulin promoter upstream of BAPTM (FIG. **27**B). These mice will be crossed resulting in TRPV1 and BAPTM expression exclusively in beta cells (FIG. **27**C). In addition, a further cross to a reporter mouse expressing luciferase downstream of NFAT response elements and a minimal promoter results in co-expression of calcium dependent luciferase (FIGS. **27**D and **27**E). Immunohistochemistry will be used to confirm TRPV1 and BAPTM expression in beta cells.

These studies aim to address whether NICE can be employed to regulate endogenous insulin release in vivo without the necessity of injecting cultured cells. At 8-10 weeks, transgenic mice will receive pancreatic injections of iron oxide nanoparticles or vehicle. Nanoparticle binding to beta cells will be confirmed using double IHC for insulin and streptavidin. It has been established that the 20 nm particles that will be used can freely diffuse in tissues. Once the optimal time for particle binding to the cells has been determined, the effect of RF field stimulation on blood glucose and insulin will be examined. A luminometer will be used to examine the luciferase response to RF stimulation in vivo as previously shown by us. The effects of RF field power and duration on these parameters will be studied at various times (see above). When these parameters have been optimized, mice also will undergo glucose tolerance testing in the presence or absence of RF stimulation. Pending these results, these studies will be repeated on control and InsTRPV1-BAPTM mice treated with streptozocin (a model of insulin deficient diabetes), high fat diet (a model of insulin resistant diabetes) or transgenic mice crossed to leptin deficient, glucose intolerant, ob/ob mice.

Combinatorial Activation of Nanoparticles to Regulate Glucose Metabolism In Vivo. Combinatorial activation of nanoparticles can be applied to develop a system whereby circulating glucose can be modulated through the release of either insulin or glucagon. PC12 are stably transfected to give two populations, the first expressing TRPV1 modified with a His6× tag and NFAT driven insulin expression (PC12-TRPV1His-Ins) and the second expressing TRPV1 modified with a FLAG tag and NFAT driven glucagon expression (PC12-TRPV1FLAG-Glucagon). A combination of the two cell lines are then injected subcutaneously into nude mice to give a tumor with a mixed cell population of both PC12-TRPV1His-Ins and PC12-TRPV1FLAG-Glucagon which can be confirmed by IHC for His and Flag epitopes. The tumor is then injected with a cocktail of iron oxide nanoparticles functionalized with anti-His6× antibody and gold nanoparticles functionalized with anti-FLAG antibody. RF stimulation at 465 kHz should heat iron oxide nanoparticles and stimulate PC12-TRPV1His-Ins cells to synthesize and release insulin reducing plasma glucose since gold nanoparticles are not heated at this lower frequency. RF stimulation at 13.5 MHz preferentially heats gold nanoparticles targeted to activate PC12-TRPV1flag-Glucagon cells to release glucagon and increase plasma glucose. Finally, alternating 10 minute pulses of RF frequencies of 465 kHz and 13.5 MHz using a variable frequency amplifier will be used to stimulate the release of both glucagon and insulin to modulated plasma glucose. These studies allow one to confirm that NICE can be used to activate different cell types alone or in combination. These studies allow one to remotely up regulate or down regulate blood glucose upon which future development of artificial endocrine organs may build on. See FIGS. **10**A-**10**D for demonstration of in vivo regulation of insulin expression.

Example 5. Effects of Nice on Neural Activity In Vivo

Following optimization of NICE on neural activity in vitro, its efficacy in mice in vivo will be confirmed. To this end, the utility of NICE will be demonstrated by studying a well-characterized neural network and behavior; the dopamine reward pathway using a self-stimulation paradigm and compare its actions to those of an invasive neural stimulation protocol using channelrhodopsin and blue light. The use of channelrhodopsin has been validated to induce reward behavior, see below, and this system will be used to compare the ability of the NICE protocol to induce this same behavior.

Self Stimulation Protocol Using Channelrhodopsin. In traditional self-stimulation protocols, rodents are trained to associate lever pressing with delivery of an electrical stimulus into a specific brain region. The behavioral chamber consists of a choice between two levers, one lever results in direct brain stimulation while the other has no effect. A decreased latency to lever press and increased frequency of lever presses indicates stimulation of the brain region is rewarding to the animal. Using such a protocol, it has been demonstrated that stimulation of the ventral tegmental area (VTA), rich in dopamine neurons, is rewarding (Fibiger H C, 1987 J Neurosci 7:3888-3896; Druhan J P, Fibiger H C, Phillips A G 1990 Behav Brain Res 38: 175-184)(8, 9)(8, 9)

Recently, a modified version of this self stimulation protocol has been validated using a lickometer to trigger light dependent opening of channelrhodopsin and thus specific activation of dopaminergic neurons. The lickometer places a sipper tube behind a ">" shaped plate such that the mouse is forced to lick for water delivery. An infrared beam placed between the plate and the sipper counts each beam break by the tongue as the animal licks for water. In these

studies, the operant behavior is consumption of water from the lickometer under conditions where the mice have a choice between one lickometer port which has no effect, and a second port which results in light delivery activating VTA neurons that express ChR in dopamine transporter (DAT) cre cells. This system confers anatomical specificity by expressing the effector, channelrhodopsin (ChR2), only in a defined neural population i.e.; the dopaminergic neurons expressing a DAT-cre construct expressed in these neurons. The scheme for this experiment is shown in FIGS. **28**A-**28**F. In studies using this system, mice with dopamine neuron specific expression of ChR2 show a significant increase in consumption from the light-activating lickometer port (FIGS. **28**A-**28**F). This paradigm provides a means for comparing the robustness of light vs. RF for neural activation of this reward behavior.

Self Stimulation Protocol Using NICE. The effects of NICE on dopamine neuron excitation will be directly compared with those already achieved by optogenetic stimulation mediated by channelrhodopsin (ChR2). In this manner, a baseline stimulation is provided that is achieved currently using invasive light activation and allows one to assess the efficacy of RF stimulation. Stereotactic injection of Ad-FLEX-NICE or AAV-FLEX-ChR2 encoding cre-dependent constructs into the VTA of DAT-cre mice will be used to drive specific expression of NICE constructs (TRPV1 and BAPTM), ChR2-mCherry or mCherry alone (control) in the dopamine neurons of DAT cre mice.

Ten days after virus injection, ChR2 injected and control mice will be implanted with a fiber optic system to deliver blue light (473 nm wavelength) to the VTA and allowed to recover prior to training. NICE mice and a second group of control mice will receive a VTA injection of streptavidin-coated iron oxide nanoparticles. The location of the nanoparticle injection will be confirmed by MRI, which can be used to precisely localize the beads. The distribution of particles on dopaminergic neurons will also be analyzed using double IHC for streptavidin and dopamine.

Following acclimation to the behavioral equipment (Med Associates), mice will be given three daily 60 min training sessions to establish the association between one of two lickometers (L-A or L-B; counterbalanced) and intracranial stimulation either via a pulse of blue light (ChR2) or a pulse of RF field (NICE). For half the animals, L-A will be rewarded and L-B unrewarded and for half, L-B will be rewarded and L-A unrewarded. Consumption from the lickometer at each training session and at testing will be recorded by the infrared monitoring system. Having acquired the association between the lickometer and delivery of light or RF field, retrieval will be tested 2 days after training. The latency to consumption and the number and pattern of licks will be recorded over a 2 h trial period. A decreased latency and increased frequency to lick at the port associated with RF delivery would suggest that NICE is capable of activating DAT cre neurons to modify reward behavior. At the end of the study, mice will be sacrificed and specific expression of TRPV1-BAPTM (anti-TRPV1, anti-tyrosine hydroxylase (TH) and Alexa-streptavidin) or ChR2 (mcherry, anti-TH) in the DAT neurons confirmed by immunohistochemistry.

As with in vitro studies, the RF field will heat metal and therefore the behavioral equipment must be free of all metal components. This will be achieved by using a custom-built plexiglass chamber with glass sippers and fiber optical cabling delivering information from the infrared beam break system. A video system mounted above the RF field will monitor movement in the chamber. The chamber will be encircled by a custom-made coil sufficient to provide a uniform RF field throughout the chamber and to a height equivalent to that of a rearing mouse.

Overall, this set of studies will confirm that RF field stimulation is effective at neural stimulation to modify behavior in vivo in vertebrates. It also will allow comparisons of the ability of NICE to activate dopamine neurons for self-stimulation in comparison to light stimulation via ChR2. Additional studies may be performed to optimize the field strength and duration of the individual stimulus delivered with each response and thereby create response-field strength curves and response-duration curves. These studies will allow optimization of the NICE system in vivo in a well-defined paradigm alongside existing stimulation tools.

Combinatorial Activation of Nanoparticles to Study Feeding Behavior In Vivo. The use of NICE is most advantageous for the study of complex behaviors where intracranial implants and tethering to deliver light or electrical stimuli may subtly alter or hinder behavior. One such behavior is feeding, which is particularly susceptible to interference such that even relatively low levels of stress may alter feeding patterns (Abbott C R et al. 2006 Int J Obes (Lond) 30:288-292). The hypothalamus regulates feeding to maintain body weight in a narrow range while hedonistic systems, particularly dopamine reward pathways and cortical regions, modulate and may even over-ride this (Davidson T L 1993 Psychol Rev 100:640-657). The hypothalamic arcuate nucleus is known to be a key component of hypothalamic feeding circuitry. The arcuate contains two primary cell populations expressing the leptin receptor, one co-expressing neuropeptide Y (NPY) and agouti related peptide (Agrp) and the second co-expressing the gene pro-opiomelanocortin (POMC) whose major product is alpha melatonin stimulating hormone (a-MSH) (Cone R D, 2001 Int J Obes Relat Metab Disord 25 Suppl 5:S63-S67) Central and arcuate Agrp injection potently stimulates feeding, knock-down in Agrp expression reduces body weight and postnatal loss of Agrp neurons reduces food intake and body weight (Bewick G A et al. 2005 FASEB J 19: 1680-168; Gropp et al. 2005 Nat Neurosci 8:1289-1291; Rossi M. et al. 1998 Endocrinology 139:4428-4431; Makimura H. et al. 2002 BMC Neurosci 3: 18). Conversely, central administration of a-MSH inhibits feeding and mice lacking the MC4 receptor, at which a-MSH is an agonist are hyperphagic and obese (Shimizu H, et al 1 989 Life Sci 45:543-552; Huszar D. et al. 1997 Cell 88: 131-141). However, these neurons also express classical neurotransmitters and other neuropeptides whose effects may not be reflected in the pharmacological approaches of intracranial peptide delivery or peptide overexpression. Further, the relative dominance of these neural populations on feeding is unknown for example, whether stimulation of Agrp neurons outweighs the effect of stimulating POMC neurons or vice versa. Until now, the technology has not been available to acutely stimulate defined cell populations and examine the consequences in freely moving animals. Therefore, NICE will be used to selectively stimulate these important neuronal populations in vivo, either individually or together, to examine their physiological roles in feeding.

BAC transgenesis will be used to generate mice expressing epitope-tagged TRPV1 channels directly under the control of the Agrp promoter (His tagged) or the POMC promoter (FLAG tagged) (FIGS. **11**A-**11**E) (Gong S et al. 2002 Genome Res 12: 1992-1998). When these mice are crossed, dual transgenic progeny expressing Agrp-Trpv1His and POMC-Trpv1FLAG will be generated (FIG. **29**C). Specific expression will be confirmed by dual IHC for

His/Agrp and FLAG/a-MSH. Mice will receive a stereotactic injection into the arcuate nucleus of a mixture of anti-His coated iron oxide nanoparticles and anti-Flag gold nanoparticles. These will bind specifically to Agrp neurons and POMC neurons respectively. The effects of neural stimulation on food intake will be determined in a custom built, metal-free metabolic chamber (Columbus Systems). A coil surrounding the chamber will generate a variable RF field and the pattern, frequency and total food intake will be examined along with feeding related behaviors such as activity.

First, feeding behavior in response to stimulation of individual neural populations will be examined. The effects of Agrp neuron stimulation will be examined in the presence of RF field stimulation at 465 kHz to heat iron oxide particles (FIG. **29**E). The effects of POMC neuron stimulation will be with RF stimulation at 13.5 MHz which selectively heats gold nanoparticles (FIG. **29**F). Finally, combinatorial stimulation will be achieved by pulsed alternating RF stimulation at 465 kHz and 13.5 MHz (FIG. **29**G). These studies will provide important data regarding the physiological roles of these two neural populations. Overall, these studies will employ NICE to dissect the contribution and the interaction of specific neuronal populations to a complex behavior, feeding, in freely moving animals. These studies also provide a basis for using the method to probe the role of other neural populations to control feeding and other behaviors.

In summary, a combination of nanoparticle heating in an RF field with defined expression of a cell surface tag for targeted nanoparticle binding will be used together with a temperature responsive ion channel to convert localized temperature changes into remote, temporally controlled and anatomically defined cell activation. Using the current in vitro system validation of this technique has been conducted to show that NICE results in a significant increase in intracellular calcium and can thereby stimulate calcium dependent gene expression. The cellular responses to NICE will be examined and validation combinatorial cell activation. The novel technology will be used to modulate hormone release in vitro and in vivo and to modify neural activity in vitro and in vivo to investigate feeding behavior. Together these studies will further support the use of NICE as a tool for external, non-invasive, specific cell excitation and the employment of NICE as a unique methodology to investigate the effects of specific cell stimulation.

Example 6. Cell Based Nanoparticle Therapy for Diabetes

Transfecting cells with the ferritin construct resulted in the distribution of nanoparticles throughout the cell cytoplasm and with an average distance of the ferritin nanoparticle to the TRPV ion channel approximately equal to the cell radius. Previous mathematical modeling predicts that particles within 200 nm would lead to sufficient heating to trigger channel activation (Huang et al., Nat. Nanotechnology 5:602-606). The number of ferritin nanoparticles were therefore quantified within 200 nm of the cell membrane by EM. It was found that there are 12.6±2.86 particles per 0.2 μm^2 with an average distance to the cell membrane of 60.3±2.85 mn. This distance is not dissimilar from the average distance between nanoparticles bound to transmembrane biotin acceptor protein tether (100 nm). Assuming the ferritin particles are evenly distributed through the cell, this would give 5×10^8 ferritin particles/cm^3. This is in considerable excess of the 1.1 pg of iron (5×10^5 nanoparticles assuming ferritin has a similar composition to iron oxide nanoparticles but 10 nm diameter) calculated to be necessary to achieve a 5° C. increase in temperature.

Results

Diseases related to tissue loss have traditionally been treated by pharmacological replacement of cell secretory products, such as insulin or dopamine, and more recently by organ or cell transplantation from cadaveric donors. Pharmacological therapies often have side effects and effective means of delivering peptide drugs in particular are limited. However, more physiological treatments such as allogenic cell implantation are hampered by lack of donors and the necessity of long term immunosuppression. Therefore, a technique which allows precise, remote activation of defined cells to trigger gene expression and peptide release in vivo offers potential as a cell replacement therapy as well as a tool for basic research.

The importance of developing means for activating specific cells has been widely appreciated as evidenced by the use of direct stimulation through implanted electrodes. However this approach is limited by variable activation, the need for permanent implants, and tissue damage. In addition this technique does not allow selective activation of specific cells. An alternative approach makes use of drug inducible systems to alter gene expression or ion channels to modulate cell activity. While drug inducible gene expression systems do allow cellular specificity, they typically have a relatively slow onset of action. In contrast, ion channels rapidly regulate intracellular ion concentrations by allowing the selective passage of cations or anions, and in turn modulate intracellular functions in a cell specific manner. The use of ion channels has many advantages; their structure and function are relatively well described, they have a rapid time course of activation and a broad range of channels exist in mammalian and non-mammalian cells, which may be exploited in the search for the optimum means of modifying cellular activity. Recently, the non-mammalian channelrhodopsin (ChR2) gene, a light activated cation, has been employed to rapidly activate molecularly defined neurons when exposed to blue light. This system gives anatomical specificity and temporal control but requires fiber optic light delivery via invasive chronic implanted devices because light penetration is relatively poor. Thus a means for activating ion channels without the requirement of an implanted device could represent an important potential means for activating cells. Describe herein is a means for non-invasive excitation of a defined cell population in vivo using a radiofrequency field to heat iron oxide nanoparticles which in turn activate the temperature sensitive TRPV1 channel to trigger calcium entry. Calcium influx in turn activates gene expression and in the current system, hormone release. This approach has been validated by modulating the expression and secretion of the peptide hormone, insulin, and shown that it can be used to lower blood glucose in mice.

Remote activation of cells using metal nanoparticles and an epitope tagged temperature sensitive channel. In order to activate cells and tissues non-invasively, it is necessary to have a signal that is capable of passing through tissue. Radiofrequency (RF) signals at low and medium frequencies penetrate tissues freely and without significant energy absorption. In contrast, metallic/metal oxide nanoparticles placed in an alternating RF field absorb energy and heat in a controlled manner dependent on particle size (FIGS. **12**A-**12**D) and the field strength. In vitro, the temperature response achieved is fast and decays quickly (inverse of the

square of the distance) thus potentially providing a rapid, highly localized 'on-off' switch. Metal nanoparticles can readily be functionalized to target to defined cell populations by coating with specific antibodies that recognize proteins that are normally expressed on a cell or transfected into that cell. Thus, nanoparticles are well suited for inducing cell surface temperature changes that can be transduced into cellular responses by temperature sensitive channels in vitro and in vivo.

The local temperature change achieved by exposing nanoparticle-coated cells to radio waves can be transduced into calcium entry by targeted expression of TRPV1 channel. This single component, cell surface cation channel detects small changes in temperature just above the physiological range (>42° C.) and undergoes a conformational change allowing calcium entry. The response is proportional to the temperature change and relatively rapid, thus transducing temperature variations induced by the heated nanoparticles into a graded calcium current with attendant cell activation. In addition these channels do not desensitize after repeated activation as repeated heating potentiates calcium entry.

The method described herein makes use of metal nanoparticles, directed to specific cells, and TRPV1 ion channels to remotely stimulate cell activity and gene expression as follows. A single construct encoding TRPV1, modified to incorporate a unique extracellular His×6 epitope tag was expressed in specific cells (TRPV1His). Iron oxide (TO) nanoparticles functionalized with monoclonal antibodies against the His×6 epitope tag are targeted to these cells. In the presence of a RF field, local heating of IO nanoparticles above the threshold for TRPV1 channel activation (42° C.) triggers calcium entry and cell activation (FIG. **1**). The increase in intracellular calcium then activates gene expression under the control of a calcium dependent NFAT promoter in which the calcium activated protein serine/threonine phosphatase, calcineurin, dephosphorylates the regulatory domain of NFAT, (nuclear factor of activated T cells), allowing its translocation into the nucleus where it activates the transcription of genes downstream of NFAT response elements.

Reports have described a two component system using a biotinylated transmembrane protein as a nanoparticle anchor and a separate TRPV1 to induce calcium entry, hereafter called VI BAP (FIG. **8**A). A single component system was benchmarked against this dual component system and both systems were used to control gene expression and hormone release in vitro before using the novel single component system to regulate gene expression and hormone release in vivo.

Nanoparticle decoration of cells in vitro. A modified TRPV1 channel was used as both a nanoparticle tether and effector. A short epitope tag, His×6, was introduced into the first extracellular loop of TRPV1. Modification did not significantly alter the temperature sensing ability of TRPV1 (FIG. **31**). This site is exposed to extracellular signals but distant from putative temperature and voltage sensing sequences and the pore region of TRPV1. Modifying the channel to act as the tether offers several advantages. Firstly, by increasing the proximity of nanoparticle binding and temperature sensing the effect of heat dissipation from the nanoparticle is reduced. This may reduce the density of nanoparticle binding required to achieve TRPV1 opening. Secondly, a single construct is readily targeted to defined cell populations using defined promoters. Finally, conditional expression can be controlled by recombinases such as cre or Flp.

Functionalized iron oxide nanoparticles were used to decorate the cells. Size dependent heating of IO nanoparticles occurred at 465 kHz with maximum heating achieved using an aqueous solution of 20 nm diameter particles. With an alternating magnetic field (465 kHz,), an increase of up to 17° C. can be achieved in a suspension of 20 nm iron oxide particles (1 mg/ml) (FIG. **2**A) with an initial heating rate of 0.15° C./s. A 5° C. rise in nanoparticle temperature above body temperature is sufficient to open TRPV1 channels and can be reached in 30 s. Nanoparticles of this size are within the limits of the extracellular space and therefore able to diffuse. IO nanoparticles (20 nm) functionalized with monoclonal anti-His antibody bind to $TRPV1^{His}$ expressed in transfected human embryonic kidney (HEK 293) cells. There is a significant increase in nanoparticle binding in cells transfected with TRPV1His (19.78±2.23 nanoparticles per mm cell membrane) compared to untransfected cells (2.85±0.32 nanoparticles per mm cell membrane) (FIGS. **30**A and **30**B) and greater than the density achieved with streptavidin functionalized IO nanoparticles bound to cells expressing the two component system, TRPV1 BAP (9.07±2.85 nanoparticles per mm cell membrane). In these studies, the results of the one component system (an epitope tagged TRPV1) was compared to a previously published two component system that uses a biotinylated transmembrane protein as a nanoparticle anchor and a separate TRPV1 to induce calcium entry, hereafter called VI BAP (FIG. **8**A) were compared. This two component system has been tested in vitro.

Nanoparticle activated insulin expression and release in vitro. In order to assess the potential anti-diabetic effects of this system, the modified TRPV1 construct and an NF AT-insulin construct was introduced into PC12 cells as well as 293T cells. These cells process and secrete proteins in response to increased intracellular Ca++. A synthetic promoter comprised of three calcium response elements: serum response element (SRE), cyclic AMP response element (CRE) and nuclear factor of activated T-cell response element (NFAT RE) and a minimal promoter were cloned upstream of a modified, furin sensitive insulin cDNA (FIG. **19**A). Processing of proinsulin to insulin relies on two beta cell specific prohormone convertases so a modified human proinsulin with engineered furin cleavage sites was used. This expressed protein is processed to mature insulin in non beta cells both in vitro and in vivo (Shifrin et al., gene Ther. 8: 1480-1489) and its release can be differentiated from endogenous murine insulin release in vivo. Like beta cells, cells expressing furin sensitive insulin synthesize both proinsulin and insulin and the ratio of proinsulin to insulin varies both with cell type and basal vs activated state.

HEK 293t cells expressing calcium dependent human insulin and either TRPV1His or TRPV1 BAP were decorated with functionalized IO nanoparticles. Applying a RF magnetic field to nanoparticle-decorated cells expressing TRPV1His or TRPV1 BAP and calcium regulated furin sensitive insulin significantly increased proinsulin release (FIG. **19**B) (TRPV1His: control 100±13.94% basal, RF treated 671±234.9% basal. TRPV1 BAP: control 100±23.96% basal, RF treated 477.4±136.1% basal) and insulin gene expression (FIG. **19**C) (TRPV1His: control 1.0±0.18, RF treated 2.20±0.53 relative gene expression, $p<0.05$. TRPV1 BAP: control 1.0±0.06, RF treated 2.06±0.38 relative gene expression, $p<0.05$). The increases in proinsulin release are blocked by the non-specific TRP channel inhibitor, ruthenium red (FIG. **19**B). There was a trend towards an increase in proinsulin release after 15 mins of RF treatment, presumably initially through the release of

preformed insulin containing vesicles and with a significant increase in release at 1 hour (FIG. **19**D), whilst insulin gene expression begins to increase after 45 minutes and also becomes significant at 1 hour (FIG. **19**E). This time course is similar to the expression of c-fos, a gene whose expression is also calcium dependent.

The effects of RF dependent heating of 10 nanoparticles were confined to decorated cells since there was no release of proinsulin when cells expressing BAPTM as a nanoparticle tether are mixed with, and therefore adjacent to, cells expressing TRPV1 and calcium regulated furin sensitive insulin (FIG. **19**F) (Proinsulin release: control 100±78% basal, RF treatment 109±38.2% basal). Proinsulin release only occurs when all components of the system are present: TRPV1, nanoparticles and RF magnetic field. No significant increase in proinsulin release was observed in HEK 293t cells decorated with IO nanoparticles in the presence of an RF magnetic field without TRPV1 (transfected with BAP only), in cells with TRPV1 but without nanoparticle binding (transfected with TRPV1 only), or in cells with nanoparticles and TRPV1 ($TRPV1^{His}$ or TRPV1 BAP) but in the absence of the RF magnetic field (FIG. **32**).

To assess cell viability, immunohistochemistry was used to quantify two markers of apoptosis-active caspase 3 and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL). No differences in immunopositive cell counts were observed between TRPV1 His transfected 239t cells treated with nanoparticles alone and those treated with nanoparticles and RF magnetic field application (FIGS. **19**G and **19**H) (TUNEL: control 123±37 cells, RF treatment 124±17 cells. Activated Caspase-3: control 136±21 cells, RF treatment 163±11 cells).

Nanoparticle regulation of blood glucose in vivo. Experiments were conducted to translate in vitro findings in vivo by testing whether the remote activation of proinsulin gene expression, insulin synthesis and release could modulate blood glucose in mice. Stably transfected PC12 cells expressing $TRPV1^{His}$ and calcium regulated furin sensitive insulin were established. As above, this endocrine cell line is capable of synthesizing and secreting mature insulin. In vitro studies examining the effects of RF treatment on proinsulin release and insulin gene expression replicated the findings in transfected HEK 239t cells (FIGS. **33**A-**33**C). Stably transfected PC12-TRPV1His-Ins cells were injected subcutaneously into the flank of nude mice and formed tumors expressing TRPV1His (FIG. **33**D) and furin sensitive insulin constructs. Following an overnight fast, PBS or 10 nanoparticles were injected into the tumors of anesthetized mice (50 μl total volume, nanoparticle concentration 8 mg/ml). Blood glucose and plasma insulin were measured before, during and after the application of an RF field (See FIG. **33**E). Applying the RF magnetic field resulted in significant decrease in blood glucose in mice treated with 10 nanoparticles compared with those receiving PBS followed by RF treatment (FIG. **10**A) (Δ Blood glucose at 30 mins: PBS control −10.99±9.72, nanoparticle treated −53.62±8.90, $p<0.05$. At 45 mins: PBS control −9.74±8.52, nanoparticle treated −60.88±11.59, $p<0.05$. At 60 mins: PBS control −6.24±15.29, nanoparticle treated—−55.12±13.15, $p<0.05$). There was a significant difference in the cumulative change in blood glucose between PBS and nanoparticle treated mice over the course of the study (FIG. **10**B) (TRPV1His, NF Ins AUC (0-120 min): PBS treated 271.7±691.6, nanoparticle treated −2695±858.3 mgdl-1 min, $p<0.05$). Plasma insulin was also significantly increased in mice receiving nanoparticle injection and RF magnetic field treatment but remained unchanged in control mice injected with PBS (FIG. **10**C) (Plasma insulin: PBS (−30 min) 1.83±0.38 μIU/ml, PBS (30 min) 1.75±0.36 μIU/ml, nanoparticles (−30 min) 2.26±0.76 μIU/ml, nanoparticles (30 min) 3.25±0.64 μIU/ml, $p<0.05$). In addition, proinsulin mRNA levels were significantly higher in nanoparticle injected tumors treated with RF magnetic field compared to those injected with nanoparticles alone (FIG. **10**D) (Control: 1.0±0.2 relative insulin gene expression, RF treated: 2.03±0.3 relative insulin gene expression, $p<0.05$). There was no difference in apoptosis, assessed as before by TUNEL and activated caspase-3, between nanoparticle injected tumors in the presence or absence of the RF magnetic field (FIGS. **10**E and **10**F) (TUNEL: control 56.4±9.8 cells, RF 48.8±8.9 cells. Active Caspase 3: control 199.8±27.4 cells, RF 168±24.4 cells)

To ensure the effects on blood glucose were not the result of non-specific release of insulin due to thermal effects of nanoparticles on the tumor, the in vivo study was repeated using PC12 cells established to stably express calcium regulated furin sensitive insulin alone without TRPV1His and it was found that there was no significant effect on blood glucose in mice injected with PBS or nanoparticles with RF magnetic field application (FIGS. **12**A-**12**D). Nor was there a cumulative change in blood glucose (FIG. **10**B) (NF Ins AUC (0-120 min): PBS treated 1851±1126 mgdl-1 min, nanoparticle treated 1281±1758 mgdl-1 min) or in plasma insulin levels (Figure IOC) (Plasma insulin: PBS (−30 min) 1.77±0.31 μIU/ml, PBS (30 min) 1.31±0.15 μIU/ml, nanoparticles (−30 min) 1.2±0.17 μIU/ml, nanoparticles (30 min) 1.17±0.23 μIU/ml). Finally, there was no difference in proinsulin mRNA expression between nanoparticle-injected NF Ins tumors with or without RF magnetic field treatment (FIG. **10**D) (Control: 1.0±0.4 relative insulin gene expression, RF treated: 1.0±0.2 relative insulin gene expression). Intratumoral temperatures did not differ between RF treated PC12 TRPV1His-Ins and PC12 Ins tumors (FIGS. **12**B and **12**C). Thus the release of insulin and lowering of blood glucose requires the presence of the particles, the modified TRPV1 channel and the NFAT-insulin construct. These findings demonstrate that magnetic field heating of nanoparticles coupled to TRPV1 activation remotely and specifically regulates proinsulin mRNA synthesis and insulin release to reduce blood glucose.

The development of a cell based system for remotely activating cells and its utility for lowering blood glucose in mice is demonstrated herein. There have been relatively few advances in the therapies available for diseases caused by tissue loss—the mainstay of treatment remains pharmacological replacement often with marked side effects. Remote modulation of cell activity and downstream functions such as gene expression, protein synthesis and secretion combined with developments in stem cell therapy offers the prospect of more physiological therapies in the form of engineered autografts. Nanoparticle dependent calcium entry could be used to regulate not only hormone release but also functions such as neural activity or muscle contraction.

The system described herein can be further modified to achieve combinatorial activation of different cells. Cell populations expressing TRPV1 engineered to incorporate unique epitope tags could be decorated with different nanoparticles designed to heat in response to distinct RF frequencies allowing combinatorial cell activation and peptide release. For example, gold nanoparticles, could be labeled with a second antibody to a different epitopes on the modified TRPV1 channel in cells engineered to express glucagon. This would enable one to either lower or raise blood glucose depending on the ambient blood glucose concentration.

These studies provide a platform for developments using different types of nanoparticles with enhanced characteristics. For example, refinements in nanoparticle structures could be used to depolarize cells without the need for a TRP channel; this advance would allow the direct activation of cells using nanoparticles with antibodies directed against specific cell surface epitopes. It may also be possible to engineer cells that express nanoparticles intracellularly thus obviating the need for injecting particles.

The present invention is not to be limited in scope by the specific embodiments described herein which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the claims. Various publications are cited herein, the contents of which are hereby incorporated, by reference, in their entireties.

What is claimed:

1. A pharmaceutical composition comprising ferritin nanoparticles that are selective for a temperature sensitive channel or receptor, and which ferritin nanoparticles can be remotely activated in a cell type of interest, wherein the ferritin nanoparticle is a ferritin fusion protein.

2. The pharmaceutical composition of claim **1**, wherein the temperature sensitive channel is selected from the group consisting of TRPV1, TRPV2, TRPV3, TRPM8, chimeric TRP channels, and tandem pore domain potassium channels.

3. The pharmaceutical composition of claim **1**, wherein the ferritin nanoparticles are activated when a radiofrequency field is applied thereto.

4. The pharmaceutical composition of claim **3**, wherein activated comprises an increase in temperature.

5. The pharmaceutical composition of claim **1**, wherein the nanoparticles are intracellularly expressed.

6. The pharmaceutical composition of claim **1**, wherein the ferritin nanoparticles comprise a targeting moiety.

7. The pharmaceutical composition of claim **6**, wherein the targeting moiety comprises: antibody, streptavidin, or peptide.

8. The pharmaceutical composition of claim **1**, wherein the receptor is a G-protein coupled receptor.

9. The pharmaceutical composition of claim **1**, wherein the cell is a stem cell.

10. The pharmaceutical composition of claim **1**, wherein the fusion protein comprises a tag.

11. The pharmaceutical composition of claim **10**, wherein the tag comprises: a nanobody peptide, His tag, or biotin acceptor protein.

12. The pharmaceutical composition of claim **11**, wherein the tag is a His tag.

13. The pharmaceutical composition of claim **1**, wherein the ferritin fusion protein comprises a ferritin light chain fused to ferritin heavy chain.

14. The pharmaceutical composition of claim **13**, wherein the ferritin fusion protein further comprises a flexible linker region.

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ENROLLED

2024 Regular Session

HOUSE RESOLUTION NO. 292

BY REPRESENTATIVE AMEDEE

A RESOLUTION

To urge and request the Louisiana Department of Health to conduct a study on the relationship between sudden unexpected deaths of infants and children, ages two and under, and the administration of vaccinations.

WHEREAS, the health and well-being of infants and children in Louisiana is paramount to this state and its residents; and

WHEREAS, the sudden unexpected death of an infant is a tragic event that can leave families and communities with many unanswered questions; and

WHEREAS, the United States has the highest infant mortality rate amongst developed nations and research shows that Louisiana has one of the highest infant mortality rates in the nation with an estimated two thousand infant deaths over the past decade, many of which were attributed to preterm births and low birth weights; and

WHEREAS, a comprehensive understanding of the causes of unexpected infant deaths is essential for developing effective strategies to prevent such tragedies; and

WHEREAS, while vaccinations have been integrated into medical practice in an effort to prevent diseases, there is still a need to continuously monitor and study the potential impact of such preventative treatment on the health of infants and children; and

WHEREAS, House Bill No. 288 of the 2024 Regular Session sought to require coroners to include the immunization records of infants who have died in their investigations, but failed to pass, highlighting the importance of further research regarding this topic; and

WHEREAS, the Centers for Disease Control and Prevention and the United States Food and Drug Administration are committed to ensuring that vaccinations provided to the public are safe and effective; and

WHEREAS, it is the responsibility of this state and its legislature to protect the health and well-being of its youngest citizens and provide the necessary resources to address the issue of sudden unexpected deaths of infants and children, ages two and under.

THEREFORE, BE IT RESOLVED that the House of Representatives of the Legislature of Louisiana does hereby urge and request the Louisiana Department of Health to conduct a study to examine the relationship between unexpected deaths of infants and children, ages two and under, and the administration of vaccinations.

BE IT FURTHER RESOLVED that the study shall include but not be limited to an analysis of the state's immunization records in the context of sudden unexpected deaths of infants and children, ages two and under, and be submitted in the form of a written report to the House of Representatives of the Legislature of Louisiana by February 1, 2025.

BE IT FURTHER RESOLVED that the written report shall contain anonymous data evaluating immunization records in the LINKS Immunization Information System, of infants and children, two years of age or younger, who died suddenly and without explanation.

BE IT FURTHER RESOLVED that the data shall include immunization records from the 2013 calendar year to present.

BE IT FURTHER RESOLVED that the written report shall include the infant or child's age at the time of death, full immunization history, and the date of the infant or child's last immunization and its proximity to the infant or child's time of death.

BE IT FURTHER RESOLVED that the Louisiana Department of Health shall collaborate with relevant state and federal agencies and medical and public healthcare experts to ensure that its study is conducted with the highest level of scientific rigor and integrity.

BE IT FURTHER RESOLVED that this state shall allocate the necessary resources and funding to support the study required in this Resolution and that the findings be used to inform future policies and practices aimed at reducing the incidence of unexpected deaths of infants and children, ages two and under, in this state.

BE IT FURTHER RESOLVED that the study called for in this Resolution shall not be conducted unless the Legislature of Louisiana appropriates monies sufficient to cover the cost of the study.

BE IT FURTHER RESOLVED that a copy of this Resolution be transmitted to the secretary and state health officer of the Louisiana Department of Health.

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SPEAKER OF THE HOUSE OF REPRESENTATIVES